Is neurosurgery referral warranted for small brain aneurysms?

■ EVIDENCE-BASED ANSWER

The risk of rupture of a small cerebral aneurysm (<10 mm) is very low in asymptomatic patients who have never had a subarachnoid hemorrhage. Because the risk of morbidity and mortality from surgical intervention significantly exceeds that of nonsurgical monitoring for this group, primary care physicians do not need to refer patients with this condition to a neurosurgeon for clipping (strength of recommendation [SOR]: **B,** based on cohort and case-control studies). For patients managed conservatively, annual office follow-up and imaging evaluation should be considered, and is necessary if a specific symptom should arise (SOR: **C,** based on expert opinion).

■ EVIDENCE SUMMARY

Intracranial aneurysms are not rare. Based on autopsy data, prevalence has been estimated to be 0.2% to 9.9% of the population.[1] Ten to 15 million Americans may have unruptured intracranial aneurysms, most of which remain undiagnosed.[2]

Conditions leading to the diagnosis of unruptured intracranial aneurysms include:

- headache (in 36% of patients)
- ischemic cerebrovascular disease (17.6%)
- cranial nerve deficits (15.4 %)
- aneurysmal mass effect (5.7%)
- ill-defined "spells" (4.8%)
- convulsive disorder (4.2%)
- subdural or intracerebral hemorrhage (2.7%)
- brain tumor (1.7%)
- nervous system degenerative disease (0.5%).[2]

No randomized controlled trials have examined whether unruptured intracranial aneurysms should be treated surgically. In the absence of a clinical trial, the evidence to answer this question is based on observational, cohort, and case-control studies, where the risks of the natural history of the condition are weighed against the risks of surgical intervention.[3]

One study of the natural history of unruptured cerebral aneurysm included 130 patients with 161 unruptured intracranial aneurysms who were followed for a mean of 8.3 years.[4,5] This prospective investigation found that 15 patients suffered an intracranial hemorrhage. There were no ruptures of the 102 aneurysms that were ≤10 mm in diameter at the time of discovery.[4,5]

In the largest cohort study to date, patients without a history of subarachnoid hemorrhage had an overall risk of rupture of 0.05% per year over 7.5 years. This study also found that surgery-related morbidity and mortality at 1 year among patients aged <45 years was 6.5%, compared with 14.4% for those aged 45 to 64 years, and 32% for those aged >64 years.[2]

What is a Clinical Inquiry?

Clinical Inquiries answer real questions that family physicians submit to the Family Practice Inquiries Network (FPIN), a national, not-for-profit consortium of family practice departments, residency programs, academic health sciences libraries, primary care practice-based research networks, and individuals with particular expertise.
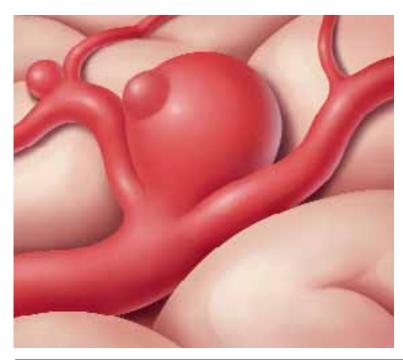
Questions chosen for Clinical Inquiries are those considered most important, according to results of web-based voting by family physicians across the U.S.

Answers are developed by a specific method:

• First, extensive literature searches are conducted by medical librarians.

• Clinicians then review the evidence and write the answers, which are then peer reviewed.

• Finally, a practicing family physician writes a commentary.

Aneurysm with daughter sac

Daughter sac formation has been associated with an increased risk of aneurysm rupture.

ILLUSTRATION BY TODD BUCK

■ RECOMMENDATIONS FROM OTHERS

The Stroke Council of the American Heart Association recommends that observation is generally appropriate for incidental, small (<10-mm) aneurysms in patients without previous subarachnoid hemorrhage. However, special consideration for treatment should be given to young patients in this group, small aneurysms approaching the 10-mm size, and aneurysms with daughter sac formation (**Figure**). In addition, patients with a family history of aneurysm or aneurysmal subarachnoid hemorrhage deserve special consideration for treatment.

For patients managed conservatively, periodic follow-up imaging should be considered; imaging is necessary if a specific symptom should arise. If changes in aneurysmal size or configuration are observed, special consideration for treatment should be made.[6]

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■ CLINICAL COMMENTARY

Asymptomatic cerebral aneurysms are potentially disastrous, since rupture can result in permanent neurologic disability or death. The diagnosis causes anxiety and fear in many patients. I try to explain to them, in clear and simple language, the minimal risk of rupture if the aneurysm is observed vs the higher risk of surgical intervention. I allow patients to express their fear and anxiety. I also elicit their input into the decision to refer. If their fear and anxiety cannot be allayed, I will refer them to a neurosurgeon. I invite them to return after the referral to discuss any further course of action.

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What findings distinguish acute bacterial sinusitis?

TABLE

Clinical prediction rule for acute bacterial rhinosinusitis

Symptoms	PPV
Local pain, unilateral predominance	41%
Purulent rhinorrhea, unilateral predominance	48%
Purulent rhinorrhea, bilateral	15%
Presence of pus in the nasal cavity	17%
Clinical prediction rule: 3/4 positive: positive likelihood ratio = 6.75, negative likelihood ratio = 0.21	

PPV, positive predictive value

■ EVIDENCE-BASED ANSWER

No combination of clinical findings can reliably distinguish acute viral rhinosinusitis from acute bacterial rhinosinusitis in primary care. Although unreliable, the best clinical predictor of acute bacterial sinusitis is the combination of unilateral nasal discharge and unilateral pain (positive likelihood ratio [LR+], 4.5; negative likelihood ratio [LR–], 0.25) (strength of recommendation [SOR]: **B**).[1] History of purulent rhinorrhea (LR+, 1.5–1.9), maxillary tooth pain (LR+, 2.1–2.5), and purulent secretions in the nasal cavity (LR+, 2.1–5.5) may increase the likelihood of acute bacterial rhinosinusitis. Illness that starts as the common cold and pain on bending forward were not predictors of acute bacterial rhinosinusitis (SOR: **B**).[2,3,4]

■ EVIDENCE SUMMARY

In one series, 87% of patients with the common cold had an abnormal computed tomography (CT) scan of the sinuses 48 to 96 hours after onset. Abnormalities visible on the CT scan persisted in 20% of patients at 2 weeks, yet epidemiological studies have shown that acute bacterial rhinosinusitis develops in only 0.5% to 2% of upper respiratory infections in adults. In primary care, only half of patients with a clinical diagnosis of acute bacterial rhinosinusitis have it proven upon aspiration.[5]

Two studies compared clinical findings with sinus puncture, the reference standard for acute bacterial rhinosinusitis. Berg found 4 independent predictors of aspirate purulence in Swedish emergency room patients with "paranasal" symptoms lasting <3 months (**Table**).[1] Together, unilateral purulent nasal discharge and predominantly unilateral pain predicated purulence on aspiration (sensitivity 79%, specificity 83%, positive predictive value [PPV], 80%). Clinical exam by an otolaryngologist had a PPV of 72%.

While emergency and primary care patients may differ, this study's rate of aspiration-proven sinusitis (43%) is closer to that seen in primary care (50%) than in referral practices (70%–80%). This study's limitations included unclear referral criteria, overlapping clinical predictors, and lack of culture data.

Only half of patients with a clinical diagnosis of acute bacterial sinusitis have it proven upon aspiration

In a study of general practice patients in the United Kingdom with clinically diagnosed acute maxillary sinusitis, no signs or symptoms were independently associated with their illness.[6] The authors concluded that the clinical examination was more or less worthless. Only patients with positive findings on CT scan underwent aspiration in this study. Less differentiated, less severe symptoms and a less stringent definition of positive aspiration in this study may account for the different results. Additionally, one third of patients eligible for this study refused participation or withdrew prior to sinus puncture.[6]

Other primary care studies used less accurate reference tests such as CT[2] (sensitivity and specificity unknown),[5] x-ray[3] (sensitivity 41%–90%, specificity 61%–85%),[5] and ultrasound[4] (sensitivity 76%, specificity 76%).[7]

Williams found 5 independent predictors of x-ray findings consistent with sinusitis in 247 male veterans:

- maxillary toothache (LR+, 2.5)
- no improvement with decongestants (LR+, 2.1)
- purulent secretions on exam (LR+, 2.1)
- abnormal transillumination (LR+, 1.6)
- colored nasal discharge (LR+, 1.5).[3]

In at least 2 of these 4 studies, purulent secretions in the nasal cavity (LR+, 2.1–5.5),[2,3] maxillary tooth pain (LR+, 2.1–2.5)[3,4] and purulent rhinorrhea (LR+, 1.5–1.9)[2,3,4] increased the likelihood of acute bacterial rhinosinusitis.

Finding purulent secretions in the nasal cavity is highly specific for acute bacterial rhinosinusitis (specificity 79%–100%)[1,2,3] but is uncommon and difficult to assess, requiring the use of a nasal speculum and possibly topical decongestants. The primary care physician's overall clinical impression was accurate in Williams' study but not in others.[2,4,6] Illness starting as the common cold and pain on bending forward were not predictors of acute bacterial rhinosinusitis.[2,3,4] Headache, bilateral maxillary pain, frontal sinus pain, fever, sinus tenderness on exam, and purulent pharyngeal discharge have not been shown to be useful in acute bacterial rhinosinusitis diagnosis.[7]

■ RECOMMENDATIONS FROM OTHERS

A recommendation from the Agency for Health Care Policy and Research suggests using symptomatic treatment initially when the prevalence of acute bacterial rhinosinusitis in patients with upper respiratory infection is <25%, and using clinical criteria (see **Table**) for acute bacterial rhinosinusitis diagnosis when prevalence is higher.[5]

The Centers for Disease Control and Prevention recommends reserving the diagnosis of acute bacterial rhinosinusitis for patients with symptoms lasting ≥7 days with maxillary pain *or* tenderness in the face *or* teeth (especially unilateral) *and* purulent nasal secretions.[8]

An otolaryngology guideline recommends considering acute bacterial rhinosinusitis when viral upper respiratory infection persists beyond 10 days or worsens after 5 to 7 days with similar symptoms.[9] The 7-to-10-day specification is based on the natural history of rhinovirus infections (SOR: **C**).

A Canadian Medical Association evidence-based review recommended a score based on Williams' 5 independent predictor symptoms:

- fewer than 2 symptoms rule out acute bacterial rhinosinusitis (PPV, <40%)
- 4 or more symptoms rule in acute bacterial rhinosinusitis (PPV, 81%) (level of evidence [LOE]: **4**)
- 2 or 3 symptoms (PPV, 40%–63%) may benefit from radiography (SOR: **C**).[10]

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■ CLINICAL COMMENTARY

This summary emphasizes inconsistencies in the literature and the limited predictive value of clinical findings when diagnosing sinusitis. But there is a way to sidestep this problem. When a patient presents complaining of "sinusitis," I ask about their expectations for the visit and their understanding of their symptoms' possible causes, and then I often show the patient a picture of sinus anatomy. By demonstrating that the osteomeatal complex is small, and focusing on *obstruction* rather than *infection,* I am able to avoid any confrontation about antibiotics entirely. Then I can recommend irrigation, hydration, and analgesia. For patients whose symptoms persist beyond 10 to 14 days, and for whom these initial interventions have failed, a trial of antibiotics may be indicated.

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Do imaging studies aid diagnosis of acute sinusitis?

■ EVIDENCE-BASED ANSWER

Accurate diagnosis of acute sinusitis in both children and adults depends on the history and clinical examination of the patient. While the clinical signs and symptoms of acute sinusitis are often difficult to distinguish from viral upper respiratory infection,[1,2] such an assessment remains the best approach to diagnosing acute sinusitis (strength of recommendation [SOR]: **A**). There is no role for imaging in the diagnosis of acute sinusitis. For patients who have persistent symptoms, or those for whom surgery is being considered, some guidelines suggest that coronal computed tomography (CT) scan of the paranasal sinuses be considered (SOR: **C,** expert opinion).

■ EVIDENCE SUMMARY

Three recent evidence-based guidelines[3,4,5] suggest that children and adults with acute sinusitis may benefit from treatment with antibiotics more than those with rhinitis. Clinicians must develop a strategy for accurately diagnosing sinusitis to make sound treatment decisions. In the absence of a clear diagnosis of acute sinusitis, antibiotics are very unlikely to improve symptoms and are, therefore, not indicated.

Clinical evaluation. Berg[1] studied 150 patients with clinical diagnoses of sinusitis and found that 85% of them had positive sinus puncture. In a review of the 11 studies that met evidence-based inclusion criteria, Varonen[6] concluded that clinical evaluation has a sensitivity of roughly 0.75, whereas radiographic methodologies have sensitivities >0.80. In a prospective trial and subsequent review of the literature, Lindbaek[7,8,9] suggests that several key clinical signs and symptoms can provide a level of sensitivity that approaches that of CT or magnetic resonance imaging (MRI), while enhancing specificity:

TABLE

Sensitivity and specificity of imaging modalities in sinusitis

Diagnostic technique	Sensitivity	Specificity
X-ray	Variable	Variable
CT scan	High	Poor
MRI	High	Poor
Sinus puncture	High	High
Clinical evaluation	High	Moderate

- Purulent secretion reported as a symptom or found in the nasal cavity by the doctor
- Pain in the teeth
- Pain on bending forward (inconsistent findings between studies)
- Two phases in the illness history
- Elevated erythrocyte sedimentation rate or increased C-reactive protein
- Symptoms for at least 7 days

Lau and colleagues[5,10] reviewed 14 studies that compared various imaging studies with clinical evaluation or sinus puncture and aspiration with culture or both. A positive aspirate for bacterial pathogens was defined as the gold standard for diagnosis of sinusitis (**Table**).

X-ray vs sinus puncture. Depending on the criteria used to define a diagnosis of sinusitis on plain radiograph, estimates of sensitivity in these studies ranged from 0.41 to 0.90, and specificity estimates ranged from 0.61 to 0.85. Imaging studies that included "mucous membrane thickening" as a criterion for sinusitis were more sensitive but less specific than studies defining positive radiographs as "opacification of sinus."

CT scan, MRI, ultrasound. While a CT scan is more sensitive than plain x-ray film,[11] and MRI is more sensitive than a CT scan,[12,13] the specificity of these studies is unclear. For example, in children and adults without symptoms of sinusi-

tis, the prevalence of sinusitis signs on CT and MRI is 45% and 42%, respectively.[6,7,14] In light of such findings, these imaging methodologies are better reserved for patients in whom surgery is being contemplated, or for whom chronic sinusitis is a concern. In the 1980s and 1990s, ultrasound was studied enthusiastically. Variability in test performance is great.[6] Since the cost of this procedure is similar to that of a sinus CT, ultrasound is not indicated in the diagnostic evaluation of the sinuses.

Though the sensitivity and specificity of a clinical evaluation possibly could be enhanced with the use of imaging studies, diagnostic accuracy of acute disease is not sufficiently improved to justify the cost or inconvenience of such interventions.

■ RECOMMENDATIONS FROM OTHERS

In a guideline on appropriate antibiotic use in sinusitis,[4] endorsed by the Centers for Disease Control and Prevention, American Academy of Family Physicians, the American College of Physicians–American Society of Internal Medicine, and the Infectious Diseases Society of America, radiography is not recommended for the diagnosis of acute sinusitis. The guideline recommends that clinicians rely on duration of illness (at least 7 days) and severity of symptoms to make an accurate diagnosis of sinusitis.

The American Academy of Allergy, Asthma and Immunology[15] guideline makes the following recommendations regarding imaging:

- The use of imaging may be appropriate when there are vague symptoms, or poor response to initial management
- Standard radiographs are insensitive, but may be used for diagnosis of acute sinus disease
- CT is preferred for preoperative evaluation of the nose and paranasal sinuses

- MRI is very sensitive for diagnosis of soft tissue disease in the frontal, maxillary, and sphenoid sinuses
- Ultrasonography has limited utility but may be applicable in pregnant women and for determining the amount of retained secretions.

The Institute for Clinical Systems Improvement recommends that radiology be used only if initial treatment has failed, and notes that a primary goal of its guideline was to reduce the number of x-rays that physicians order for this diagnosis.[16]

The American College of Radiology's criteria for sinusitis in the pediatric population ranked several radiographic studies based on their appropriateness for given clinical conditions. This review[17] suggests that no imaging is appropriate if symptoms have persisted <10 days. For patients with symptoms lasting >10 days and with persistent fever, CT scan is recommended.

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■ **CLINICAL COMMENTARY**

In acute bacterial sinusitis, the history and physical have somewhat limited sensitivity and specificity. Unfortunately, imaging studies add little valuable information. Primary care physicians must therefore be reconciled to some degree of diagnostic error.

The risks associated with under-diagnosis are small, since most cases of mild sinusitis will resolve spontaneously without treatment. The risks of over-diagnosis include increased antibiotic costs, side effects, allergic reactions, and the development of resistant organisms. It is prudent, therefore, to make the diagnosis only when multiple suggestive historical and exam elements are present and to avoid giving antibiotics to patients with mild, nonspecific illnesses.

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> The risks of under-diagnosing acute sinusitis are small, as most cases will resolve without treatment

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How effective is desmopressin for primary nocturnal enuresis?

■ EVIDENCE-BASED ANSWER

Desmopressin reduces the number of nights of primary noctural enuresis by at least 1 per week, and increases the likelihood of "cure" (defined as 14 consecutive dry nights) while treatment is continued (number needed to treat [NNT]=5–6) (strength of recommendation [SOR]: **A,** based on meta-analysis). Evidence suggests that the benefits of desmopressin are temporary, with a high relapse rate once treatment is discontinued (SOR: **B**). However, long-term therapy with occasional weaning attempts is a safe option (SOR: **B**). Evidence is inadequate to judge the relative efficacy of the nasal vs oral forms of desmopressin (SOR: **C**).

■ EVIDENCE SUMMARY

Desmopressin is an analogue of the natural pituitary hormone vasopressin acetate. It produces an antidiuretic effect, resulting in increased reabsorption of water from the kidney, a reduced volume of more concentrated urine entering the bladder, and a reduced 24-hour urine production.[1,2] Desmopressin is available in a nasal spray (10 µg/spray) and an oral tablet (0.2 mg), and is most often prescribed as 1 to 2 sprays per nostril or 1 to 3 tablets at bedtime, regardless of age or weight.[1]

A Cochrane review[1] of 16 randomized controlled trials found nasal desmopressin to be better than placebo in reducing the number of wet nights per week (mean 1.34 fewer wet nights/week; 95% confidence interval, 1.11–1.57). Desmopressin at doses of 20 µg, 40 µg, and 60 µg similarly increased the likelihood of a cure (14 consecutive dry nights during treatment) in 3 trials reporting this outcome (relative risk for failure to achieve 14 dry nights with 20 µg=0.84; NNT for cure=5.6).[3] No differ-

ence was found in cure rates after treatment was stopped. Data were insufficient to judge the effectiveness of the oral versus nasal route of desmopressin.[1]

One randomized controlled trial found a linear dose response for oral desmopressin in reducing wet nights. After 2 weeks of treatment, the number of wet nights was decreased by 27%, 30%, and 40% at doses of 0.2 mg, 0.4 mg, and 0.6 mg, respectively, compared with 10% with placebo.[1]

Snajderova and colleagues studied desmopressin as a long-term treatment for 55 children with primary nocturnal enuresis. Intranasal desmopressin was titrated upward until bedwetting stopped (7–21 µg; 89.1% responders); children in whom no response occurred to a maximum of 28 µg were excluded. Every 3 months, a weaning attempt was made; if relapse occurred, the previous successful dose was reinstated. At the end of each of the 3 years, the number of responders remained higher (72.7%, 70.9%, 61.6%) than the spontaneous cure rate of 15%.[4]

The Swedish Enuresis Trial (SWEET) demonstrated a similar outcome in an open-label study of 399 children.[5]

The main side effects of desmopressin are nasal discomfort, nose bleeds, headache, abdominal pain, rash, and (rare but serious) water intoxication. Restrict fluid to 240 mL (8 oz) on nights desmopressin is given.[1]

■ RECOMMENDATIONS FROM OTHERS

A University of California at San Diego Medical Group Guideline recommends using desmopressin for primary nocturnal enuresis in children aged >5 years when it occurs frequently and causes distress, as well as under specific circumstances, such as when a child shares a room or goes to camp, or a sleepover.

Therapy begins at 10 µg (1 nasal puff) each night, increasing weekly to a maximum of 40 µg. Younger children should be reassured, encouraged to limit fluids and void before

bedtime, partake in the responsibility to change bedding, and be praised for dry nights.[6]

The American Academy of Pediatrics also emphasizes support and encouragement of the child, and reassurance that the problem will get better in time. For children aged ≥7 years, alarm systems or bladder-stretching exercises might help.[7]

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■ **CLINICAL COMMENTARY**

Primary nocturnal enuresis can be challenging for the primary care physician, frustrating for the patient's parents, and embarrassing for the child. The physician's role is to help the child and parents realize that almost all children eventually maintain nocturnal continence whether or not pharmacotherapy is used.

Nonpharmacologic interventions, such as behavioral modification (eg, use of a nocturnal conditioning alarm with a moisture sensor) may be more acceptable to families, at least as a first attempt at therapy. In my experience, however, many children sleep through these alarms.

The decision to use medication should be made by a well-informed and motivated child and their parents. They should understand the limitations and expectations of pharmaco-therapy. The authors of this clinical inquiry have provided the physician with an excellent summary of the evidence for the efficacy of desmopressin.

Children with enuresis associated with sleep arousal disorder should theoretically respond to older forms of pharmacotherapy, such as imipramine. However, due to potential toxicity, many clinicians are reluctant to use tricyclic antidepressants in their patients. The efficacy and low toxicity of desmopressin makes it an attractive choice for pharmacotherapy in enuretic children.

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