Does injection of steroids and lidocaine in the shoulder relieve bursitis?

EVIDENCE-BASED ANSWER

Subacromial steroid injection may provide a small, short-term benefit compared with placebo. The short-term effectiveness of steroid injection compared with nonsteroidal anti-inflammatory agents (NSAIDs) remains unclear.

Steroid injections are better than physiotherapy alone in the short term. However, injection does not appear to provide any meaningful long-term benefit compared with other therapies (strength of recommendation: **B**). Data are insufficient to make recommendations regarding the proper timing of injection in the sequence of other treatments. Side effects of steroid injection, such as steroid flare and infection, are rare.

EVIDENCE SUMMARY

A Cochrane Review of corticosteroid injections for shoulder pain found 7 randomized controlled trials comparing subacromial steroid injections with placebo.[1] The placebos were either injectable anesthetics alone or injectable anesthetics combined with oral placebo tablets. Six of the 7 studies used the anterolateral approach to inject under the acromion.

All studies used a clinical exam for diagnosis that showed pain with range of motion (especially abduction) or pain that was consistent with impingement syndrome. Most of the follow-up times were short, typically 4 to 12 weeks, and the longest study was 33 weeks. Meta-analyses often report the effect size using standard mean difference (SMD). A rule of thumb for interpretation of SMD is a value of 0.2 indicates a small effect, a value of 0.5 indicates a medium effect, and a value of 0.8 or larger indicates a large effect. If the 95% confidence interval [CI] does not include zero, then the SMD is statistically significant at the 5% level ($P<.05$).[2]

Two of the studies comparing steroid injection with placebo were methodologically suitable for meta-analysis; these studies showed that steroids provided a mild, short-term (4-week) benefit with respect to pain (SMD=0.83; 95% CI, 0.39–1.26), function (SMD=0.63; 95% CI, 0.20–1.06), and abductive range of motion (SMD=0.82; 95% CI, 0.39–1.25).[3,4]

Results of the remaining, less rigorous trials were conflicting and inconclusive. The reviewers also found 3 randomized controlled trials comparing subacromial steroid injection with oral NSAIDs. The pooled results of these trials, encompassing 120 patients, found no differences

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What are Clinical Inquiries?

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 other specialists.

Questions chosen for Clinical Inquiries are those that family physicians vote as most important through a web-based voting system.

Answers are developed by a specific method:

- FPIN medical librarians conduct systematic and standardized literature searches in collaboration with an FPIN clinician or clinicians.
- FPIN clinician authors select the research articles to include, critically appraise the research evidence, review the authoritative sources, and write the answers.
- Each Clinical Inquiry is reviewed by 4 or more peers and editors before publication in *JFP*.
- FPIN medical librarians coauthor Type I Clinical Inquiries that have required a systematic search.
- Finally, a practicing family physician writes an accompanying commentary.

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in these 3 outcomes at 4 or 6 weeks. The review of an additional trial of 50 patients comparing subacromial steroid injection plus simultaneous oral NSAIDs with oral NSAIDs alone found no differences at 4 weeks. All 11 studies had small sample sizes, and suffered from variable methodological quality and heterogeneous results.

The reviewers concluded that steroids are probably better than placebo but provide little or no benefit in addition to NSAIDs, and that evidence is insufficient to guide treatment. Likewise, a Cochrane Review of multiple interventions for shoulder pain also found "little evidence to support or refute the efficacy of common interventions" and highlighted the need for new, well-designed trials.[5]

Another Cochrane Review examined 4 randomized controlled trials comparing physiotherapy interventions for shoulder pain.[6] They found that steroid injections may be superior to physiotherapy for rotator cuff disease, but the type of physiotherapy and injection sites were not consistent across the studies, making creation of summary estimates inappropriate. The individual studies showed significant short-term benefits (3–7 weeks) of steroid injection over physiotherapy; however, long-term (6–52 weeks) benefits ranged from some benefit to no difference. These studies were consistent regarding age (mean age=53–55 years, SD ± 13–14 years) and complications reported, with the only side effect being postinjection soreness.

Hay et al[7] conducted a multicenter, primary care–based randomized controlled trial with more than 200 patients, which was published too recently for inclusion in the Cochrane Review. They found no statistical difference in improvement between steroid injection without physiotherapy and physiotherapy alone at 6 weeks.

In 1996, van der Heijden et al[8] systematically reviewed randomized clinical trials of steroid injections for shoulder disorders, including rotator cuff disease, adhesive capsulitis, rheumatoid conditions, and periarthritis. They screened more than 200 articles from searches in Medline

Subacromial steroid injections are better than physiotherapy alone in the short term

(1966–1995) and EMBASE (1984–1995) and found 16 articles that met qualifying conditions for further review. Of these, 3 were methodologically adequate for final review. None of these 3 studies provided evidence showing the efficacy of steroid injections. The results of the major trials reviewed can be found in the **Table**.

RECOMMENDATIONS FROM OTHERS

The American Academy of Orthopaedic Surgeons' clinical guideline for shoulder pain[9] recommends the following for rotator cuff disease: avoidance of irritating activity; anti-inflammatory medications if tolerated; exercises to recover and maintain passive range of motion; exercises to strengthen the rotator cuff once acute symptoms abated. If these are unsuccessful over several weeks, they recommend considering subacromial injection of local anesthetic and a short-acting corticosteroid. They gave their recommendation a "B" rating (some evidence exists to suggest benefit).

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TABLE

Major placebo-controlled trials of injectable steroids for shoulder pain

Steroid (n)	Comparison	Follow-up arms (n)	Reported results	Conclusions
Methylprednisolone 1% lignocaine (28)	1% lignocaine (28)	12 wks	2 wks: insignificant improvement in steroid arm 2, 4, 6, 12 wks: no difference in pain, range of motion; all *P*>.05	No significant advantage of subacromial methyl prednisolone over lignocaine[10]
Triamcinolone, 0.5% lignocaine, placebo tabs (20)	C1: diclofenac, lignocaine (20) C2: placebo tabs, lignocaine (20)	4 wks	4 wks: steroid and C1 showed significant benefit over C2 for pain and range of motion (*P*<.05) Steroid vs C1: no difference (*P*=.0268)	Triamcinolone and diclofenac are equivalent, and superior to placebo[3]
S1: triamcinolone, 1% lidocaine, naproxen (25) S2: triamcinolone, 1% lidocaine, placebo (25)	C1: 1% lidocaine, naproxen (25) C2: 1% lidocaine, placebo (25)	4 wks	S1 superior to S2, C1, C2 S2 superior to C1, C2 For pain and clinical index at 2 and 4 wks, *P*<.05	Triamcinolone and naproxen superior to placebo. More severe cases see most benefit[4]
Triamcinolone, placebo tabs (15); reinjection at 3 wks if not better	Saline injection, indomethacin (15); reinjection at 3 wks if not better	6 wks	Pain and global scores improved in both groups (*P*<0.05), but no difference between them (*P*>.05)	No difference between indomethacin and triamcinolone injection[11]
S1: methylprednisolone, lidocaine, placebo tabs (12) S2: methylprednisolone, NSAID (12)	C1: acupuncture (12) C2: ultrasound (12) C3: placebo tab, placebo U/S (12)	4 wks	All patients improved. No differences in pain scores or abduction measurements at 2 or 4 wks (*P*=n/a)	Painful stiff shoulder may be self-limiting condition and beneficial effect may be natural recovery[12]
Methylprednisolone, 1% lidocaine (104)	Physiotherapy (103)	6 mos, option of other therapies given at 6 weeks	No differences in disability scores 6 wks: mean difference= –.05 (95% CI, –.02 to 3.0) 6 mos: mean difference= 1.4 (95% CI, –0.2 to 3.0) (7)	Physiotherapy and steroid injection were of similar short- and long-term effectiveness for treating new episodes of unilateral shoulder pain
Triamcinolone, 1% lidocaine (19)	1% lidocaine (21)	Mean: 33 wk; range: 12–52 wk	Steroid: significant improvements of pain (*P*<.005) and range of motion (*P*<.005) vs control. No difference in activities of daily living seen (13)	Subacromial injection of steroids is effective for short-term therapy of impingement syndrome

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CLINICAL COMMENTARY:

Consider injection with anesthetic and steroid for rotator cuff impingement

Subacromial injection is an integral component of the treatment armamentarium for certain types of shoulder pathology. Diagnostically, injection of a local anesthetic such as lidocaine can help differentiate true weakness caused by a full-thickness rotator cuff tear from inhibition due to inflammation and impingement pain. Strongly consider subacromial injection with both a local anesthetic and corticosteroid for patients with true rotator cuff impingement as diagnosed by positive Neer and Hawkins signs on examination.

If injection is appropriately administered, the patient should have near-immediate and significant reduction of impingement symptoms. They may regain motion sooner and advance quicker through their initial therapy program.

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What treatments are safe and effective for mild to moderate hypertension in pregnancy?

EVIDENCE-BASED ANSWER

There is considerable debate concerning the treatment of mild to moderate essential hypertension during pregnancy. Evidence suggests that because of the potential risk of fetal intrauterine growth restriction, treatment of hypertension should be delayed until maternal blood pressure reaches 150–160 mm Hg systolic or 100–110 mm Hg diastolic, as long as the mother has no preexisting end organ damage.

Methyldopa has been the drug of choice for oral treatment, as it is the only medication to have any extended follow-up study. However, a recent meta-analysis raised the possibility of increased fetal mortality (strength of recommendation [SOR]: **A**, based on systematic review of randomized controlled trials).

Labetalol is an effective alternative, but concerns remain that treatment with any beta-blocker increases the risk that infants will be small for gestational age (SGA) (SOR: **B**, based on small randomized controlled trials with inconsistent results).

There is limited evidence that calcium channel blockers and diuretics are safe alternatives, although evidence is insufficient to prove a clear benefit (SOR: **B**, based on limited randomized controlled trials). Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), due to similar mechanisms of action, are contraindicated in pregnancy (SOR: **B**, based on multiple case studies). No other class of antihypertensive medications is proven to be harmful in pregnancy.

EVIDENCE SUMMARY

Treatment of maternal hypertension during pregnancy is based on maternal and fetal outcomes.

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Multiple meta-analyses of randomized controlled trials show that the major maternal outcomes improved by treating mild to moderate hypertension are decreased progression to severe hypertension (number needed to treat [NNT]=12; 95% confidence interval [CI], 9–17) and decreased need for additional antihypertensive therapy.[1,2] The relative risk (RR) for preventing preeclampsia was 0.99 (95% CI, 0.84–1.18). The risk of preterm delivery was 1.00 (95% CI, 0.87–1.15).

The data for fetal outcomes are important, as the maternal benefits of treatment remain small.[3] Much of the debate centers on decreasing uteroplacental perfusion, which may lead to decreased fetal growth. One meta-analysis reviewed 45 trials to evaluate the potential increase in SGA infants caused by any antihypertensive treatment, through quantifying the fall in mean arterial pressure. The analysis found an average decrease in birthweight of 145 g for a 10 mm Hg fall in mean arterial pressure with no increased perinatal morbidity.[4] The clinical significance of this is unclear.

In comparing one agent with another, methyldopa was the most commonly tested agent, with 14 randomized controlled trials of more than 1010 subjects demonstrating its efficacy at reducing blood pressure. Other antihypertensive agents appear better than methyldopa in terms of reducing the risk of infant mortality (RR=0.49; 95% CI, 0.24–0.99),[1] but the studies were small and used weak methods, and this finding may be due to bias.[5] Meta-analyses of beta-blocker trials show a borderline increase in SGA infants, with no related increase in perinatal mortality, as well as a decrease in the incidence of respiratory distress syndrome.[6]

Diuretics are effective antihypertensives, especially when combined with other agents, but they are known to decrease the circulating plasma volume, potentially decreasing uteroplacental perfusion. They are generally viewed as safe, as long as the mother is not already at increased risk for perfusion abnormalities (eg, preeclamptic states).[7] Calcium channel blockers, though generally regarded as safe and effective, have mostly been evaluated for use late in pregnancy, so their benefit-to-risk ratio remains uncertain.[8] ACE inhibitors and, by extension, ARBs, due to their similar mechanisms of action, are contraindicated in pregnancy, having been linked to miscarriage, fetal death, fetal renal failure, and malformation.[5,9–11]

Treatment of hypertension should be delayed until maternal BP is 150–160 mm Hg systolic or 100–110 diastolic

RECOMMENDATIONS FROM OTHERS

The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin states there is no evidence that antihypertensive treatment for mild to moderate hypertension improves maternal or fetal outcomes, even for women who are already receiving hypertension treatment at the time of pregnancy. ACOG suggests treatment may be stopped during pregnancy, or not initiated until blood pressures reach 150–160 mm Hg systolic or 100–110 mm Hg diastolic, unless the mother has underlying renal or cardiovascular disease.[9]

The National High Blood Pressure Education Program recommends the same guidelines as ACOG,[10] whereas the Canadian Hypertension Society consensus panel has chosen 140/90 mm Hg as the level at which treatment should be initiated.[11]

The *British Medical Journal* Clinical Evidence Guidelines reiterate that the evidence does not support the benefit of treating mild to moderate hypertension, except in reducing the progression to severe hypertension.[5] Methyldopa is consistently the drug of choice in all those making a specific recommendation,[9–11] although it should be noted these recommendations were published before the 2003 Cochrane Review.[1]

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CLINICAL COMMENTARY:

Benefits from treatment do not outweigh risks unless maternal BP moderately high

I have always felt uneasy with treatment of mild to moderate hypertension in pregnancy, as chronic hypertension must be differentiated from preeclampsia; and the treatments seem counterintuitive. I often see new obstetric patients well into the third trimester, and how I should initially treat an elevated blood pressure has been unclear. Adding the welfare of the unborn baby raises the stakes further.

This Clinical Inquiry helps my decision about initiating treatment, as the benefits from treatment do not outweigh the risks to mother and fetus unless the maternal blood pressure is moderately high, and the recommended thresholds for treatment are rather high for women with no end organ damage. If I must treat her, it appears the best (but not perfect) option is methyldopa.

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Are beta-2-agonists or anticholinergics more effective for treating COPD?

EVIDENCE-BASED ANSWER

Both β_2-agonists and anticholinergics appear to improve symptoms for patients with chronic obstructive pulmonary disease (COPD). Recent research indicates that adding a long-acting anticholinergic to a β_2-agonist may improve quality of life for patients with stable COPD more than the use of β_2-agonists alone.

Both drug classes increase exercise capacity and alleviate symptoms of COPD, although neither alters disease progression (strength of recommendation [SOR]: **A**). Combination therapy can lead to greater improvements in forced expiratory volume in 1 second (FEV_1) than either drug alone (SOR: **A**). However, until recently there were no convincing direct head-to-head comparisons of the 2 classes, and it is unclear whether this difference is clinically significant.

EVIDENCE SUMMARY

A review of 33 double-blind randomized placebo-controlled studies showed a significant effect of bronchodilator therapy on exercise capacity in COPD patients in about one half of studies. Anticholinergic agents had significant beneficial effects in the majority, and these effects tended to be somewhat dose-dependent. Short-acting β_2-agonists improved exercise capacity in more

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than two thirds of the studies, but long-acting agents led to mixed outcomes. The researchers identified no superior agent between the 2 classes, citing a lack of adequate studies making a direct comparison.[1]

A recent Cochrane Review comparing the short-term effects of ipratropium to β_2-agonists in changes in FEV_1 and arterial oxygen pressure (PaO_2) concluded there was no evidence that the degree of bronchodilation from ipratropium was greater than that from short-acting β_2-agonists.[2] Subjective endpoints such as dyspnea and quality of life were not assessed, and neither of the above reviews included studies focusing on long-term outcomes.

A 12-week double-blind, double-placebo-controlled parallel group study published in 2000 followed 144 patients (age 64 ± 7 years with a FEV_1 of 44 ± 11% predicted) randomized to receive salmeterol 50 µg twice daily alone, salmeterol 50 µg twice daily plus ipratropium 40 µg 4 times daily, or placebo. Patients were assessed for changes in FEV_1, daytime symptom scores, specific airway conductance, and the need for rescue medication. The study demonstrated a significant benefit from the addition of ipratropium to salmeterol in terms of reduction of airway obstruction, but not in symptom control or need for rescue medication.[3] However, no patients were randomized to receive ipratropium alone, so comparison of the relative contribution of the 2 classes is limited.

A 6-month, randomized double-blind placebo-controlled study evaluating the efficacy of salmeterol 50 µg twice daily vs tiotropium (a new long-acting inhaled anticholinergic) 18 µg once daily was published in 2002. Endpoints in 623 patients were assessed using 12-hour spirometric performance, transition dyspnea index (TDI), and the St. George Respiratory Questionnaire (SGRQ). (SGRQ is a validated disease-specific instrument designed to measure impact on overall health, daily life, and perceived well-being. It measures activity limitations, symptoms, and psychosocial impact.) Tiotropium showed superiority over salmeterol in all endpoints assessed (0.14 L increase in morning FEV_1 vs 0.09 L, 1.02 U improvement in TDI score vs 0.24, and –5.14 U improvement of SGRQ total score from baseline vs –3.54). However, it should be noted that a difference of 1 on the TDI score was necessary to suggest a clinical benefit. While the overall difference in SGQR between tiotropium and salmeterol did not reach statistical significance, the proportion of patients in the tiotropium group that reached the clinically significant threshold of 4 units improvement in SGRQ score was significantly higher than in the salmeterol group (51% vs 40%; $P<.05$).[4]

Adding a long-acting anticholinergic to a β_2-agonist may improve quality of life for those with stable COPD

In a similar study in 2003, 1207 patients were randomized to receive the above doses of salmeterol, tiotropium, or placebo. Over the course of 6 months, tiotropium was associated with a significant delay in onset of the first exacerbation compared with placebo, and overall it led to the fewest exacerbations per patient-year. Fewer hospital admissions were also demonstrated in the tiotropium group per patient-year, and the number of days that patients were unable to perform usual activities was lowest for the tiotropium group. Again, improvement in TDI and SGRQ scores was significantly greater with tiotropium than placebo. In almost all outcomes, the salmeterol results were intermediate between those of tiotropium and placebo, and were not statistically different from placebo.[5]

RECOMMENDATIONS FROM OTHERS

The GOLD (Global Strategy for the Diagnosis, Management, and Prevention of COPD) Report states that the choice between β_2-agonist, anticholinergics, or combination therapy depends on the availability and the response of a given patient in terms of symptom relief and side effects. The 2003 GOLD Workshop Report update further recommends the use of regular treatment with

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long-acting bronchodilators, including tiotropium, rather than short-acting bronchodilators for moderate-to-severe COPD.[6]

A separate report for the Joint Expert Panel on Chronic Obstructive Pulmonary Disease of the American College of Chest Physicians and the American College of Physicians—American Society of Internal Medicine states that both are beneficial for management of acute exacerbations, but that anticholinergics should be considered first because they are associated with fewer and more benign side effects.[7]

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CLINICAL COMMENTARY:

Patient response and tolerance of side effects determine which drug class to use

Although recent national guidelines for the management of COPD, such as the GOLD report, give more cohesiveness to treatment strategies for patients with COPD, there is still room for tailoring a treatment approach. I find that when choosing between beta-agonists and anticholinergics, patient response and tolerability of side effects determine what I use.

This Clinical Inquiry supports my clinical impression that neither class of drug is significantly superior to the other in regards to COPD outcome measures. In my experience, when neither drug offers a clear advantage, factors affecting compliance and tolerability tend to determine how effective it is for my patients. Therefore, a trial of either class seems reasonable at first and follow-up determines what is used in the long run.

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Should the varicella vaccine be given to all children to prevent chickenpox?

EVIDENCE-BASED ANSWER

Healthy, unimmunized children who have not had varicella infection should be vaccinated (strength of recommendation: **A**, based on randomized controlled trials). Use of the vaccine in immunocompromised children is still being studied and has not been approved by the Food and Drug Administration (FDA).

EVIDENCE SUMMARY

Before the introduction of the varicella vaccine, almost 4 million cases of chickenpox occurred each year in the United States, resulting in 11,000 hospitalizations and 100 deaths.[1] Varicella is the leading cause of vaccine-preventable death in children.[2]

In a search of the literature from 1966 to 2000, a systematic review identified 24 randomized controlled trials and 18 cohort studies of varicella vaccination.[3] In children aged 10 months to 14

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years, 1 randomized controlled trial found protective efficacy of 100% over 9 months and 98% over 7 years.[4] A second trial showed efficacy of 72% over 29 months.[5] Cohort studies of children report that the vaccine is 84% to 86% effective in preventing varicella and 100% effective in preventing moderate to severe infections.[3]

Cumulative results of all studies show the number needed to vaccinate to prevent 1 case of varicella ranges from 5.5 to 11.8, and the number needed to prevent 1 complicated case ranges from 550 to 1180.

No direct evidence supports or refutes a reduction in varicella mortality or rates of hospitalization due to vaccination. Randomized controlled trials show no increase in rates of fever or rash among those receiving vaccine; however, cohort studies report fever (0%–36%), local injection site reactions (7%–30%), and rash (5%).[3] No clinical trials have shown transmission of vaccine-related varicella zoster virus in immunocompetent patients, and only 3 proven cases of transmission of vaccine virus to susceptible contacts have been documented.[6] Some evidence suggests the incidence of herpes zoster is reduced in immunocompromised vaccine recipients, but long-term observation is needed to assess the effect on healthy recipients.[7]

One concern about the vaccine is that waning immunity over time could result in increased incidence of varicella infection during adulthood. While existing studies document persistence of antibodies for up to 20 years following immunization,[3] long-term effectiveness should continue to be monitored.

The FDA has not approved this live-virus vaccine for use in pregnant women and immunocompromised persons, including transplant recipients and persons receiving corticosteroid therapy. However, the vaccine has been very well-studied in children with leukemia. A review of these studies found that optimal seroconversion requires 2 sequential vaccine doses (86% efficacy). A rash of varying severity was the predominant adverse event in 20% to 50% of vacinees.[7] Study of vaccine use in other immunocompromised children has been limited. Early results from a trial in HIV-infected children who were not severely immunocompromised suggests similar tolerance and efficacy compared with children without HIV.[8]

Cohort studies of children report that the vaccine is 84%–86% effective in preventing varicella

A systemic review of cost-effectiveness of varicella vaccine is based predominantly on mathematical models.[9] These models show societal savings due to decrease in unproductive days for parents, but fail to demonstrate actual healthcare savings.

RECOMMENDATIONS FROM OTHERS

The American Academy of Pediatrics (AAP), Advisory Committee on Immunization Practices (ACIP), and American Academy of Family Medicine all recommend vaccinating unimmunized children aged 12 months and older who have not had varicella infection, and not vaccinating children with cellular immunodeficiencies.[2,10,11] The AAP suggests the vaccine could be considered for children with acute lymphocytic leukemia and for HIV-infected children with mild or no signs or symptoms. The ACIP guidelines are similar, with the addition that children with impaired humoral immunity may now be vaccinated.

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CLINICAL COMMENTARY

Encourage varicella vaccination, except for the immunocompromised

For many parents, vaccination decisions are made based on school district requirements. Varicella zoster vaccine is an exception to that rule. Parents can choose to immunize their child at 12 months or wait and let nature take its course—hopefully before the child starts kindergarten. The major concern with the vaccine has been its long-term efficacy. Although no one knows for sure how long immunity is sustained, studies show that detectable antibodies are present for up to 20 years.

As a parent and physician, my decision to vaccinate my daughter was made after I witnessed an 8-year-old boy in the emergency room with respiratory distress secondary to complications from chickenpox. This experience reinforced for me that chickenpox is a life-threatening disease. The effects of chickenpox include scarring as well as time away from work for parents. I therefore encourage varicella vaccination for my patients, with the only exception being those who are immunocompromised, for whom we have no data.

To the question of whether we should we vaccinate children to prevent chickenpox, I give a resounding "yes."

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Do antibiotics prevent recurrent UTI in children with anatomic abnormalities?

EVIDENCE-BASED ANSWER

Evidence is insufficient to recommend for or against antibiotic prophylaxis to prevent recurrent urinary tract infections (UTI) in children with anatomic abnormalities. Guidelines acknowledge this lack of evidence, but still recommend using prophylactic antibiotics in children with vesicoureteral reflux (strength of recommendation: **B**, based on poor-quality or inconclusive cohort and randomized controlled studies).[1–3] No controlled, prospective studies have examined the effectiveness of prophylactic antibiotics to prevent UTI recurrence or renal scarring.

EVIDENCE SUMMARY

Recommendations about antibiotic prophylaxis are based on several premises. Reflux predisposes children to acute pyelonephritis; reflux plus infection leads to reflux nephropathy and ultimately to renal scarring. In theory, if antibiotics could be initiated at the appropriate time and be maintained until reflux resolves, we could successfully prevent infection and scarring.[4]

A recent systematic review evaluated the use of antibiotics to prevent UTI in children.[5] This review of 5 randomized controlled trials included a total of 463 children between the ages of 2 months to 16 years. Three out of 5 trials evaluated the effectiveness of antibiotic treatment for 2 to 6 months to prevent subsequent off-treatment recurrence. The 2 smaller trials (n=71) evaluated the use of low-dose long-term antibiotics to prevent UTI.

There was a clinically, but not statistically, significant trend towards reduced risk of UTI during long-term antibiotic treatment (risk reduction [RR]=0.31; 95% confidence interval [CI]=0.10–1.00); however, no sustained benefit was seen once antibiotics were stopped

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(RR=0.79; 95% CI, 0.61–1.02). There were many problems with the methodological quality of these trials, including significant heterogeneity. The researchers concluded that well-designed randomized controlled trails are still needed to evaluate this commonly used intervention in the pediatric population.[4] Benefits for long-term prophylaxis are even less clear in children with low-grade reflux (I–II).[5] Furthermore, no randomized controlled trials assess whether prophylaxis prevents the development of new renal scars in children.[6]

In addition, a recent systematic review of studies done in children with normal urinary tracts, as well in children with neurogenic bladders, found that the available evidence is of low quality. Only 6 out of 31 potential studies fulfilled the inclusion criteria. These were small (mean sample size was 28), and the quality scores of all 6 trials were low, indicating that the evidence may be unreliable.[7]

Two of 3 studies done in children with normal urinary tracts demonstrated statistically significant higher rates of UTI recurrence in control groups compared with treatment groups receiving 6 to 10 months of either nitrofurantoin or cotrimoxazole (RR=24–31). The third study showed no difference between groups.

One of 2 trials in children with neurogenic bladder demonstrated higher recurrence rates of 2.9 per 10 patient years for patients receiving antibiotics compared with 1.5 in the untreated group. The other study showed lower recurrence rates of 17.1 for patients receiving antibiotics, compared with 33 in the untreated group.[7] Neither of these findings were statistically significant.

A different meta-analysis of 15 controlled clinical trials in children with neurogenic bladder due to spinal cord dysfunction. This analysis showed that antibiotic prophylaxis was associated with a reduction in asymptomatic bacteruria among children with acute spinal cord injury ($P<.05$), but there was no significant reduction in symptomatic infections. Prophylaxis resulted in an approximately twofold increase in antimicrobial-resistant bacteria. The researchers concluded that although a clinically important effect has not been excluded, the regular use of antimicrobial prophylaxis for most patients who have neurogenic bladder caused by spinal cord dysfunction is not supported at this time.[8]

No controlled prospective studies examine the effectiveness of antibiotics to prevent UTI

Poor compliance may be an issue with long-term prophylaxis and may represent patient or parent practice.[9] One study found that in children taking low-dose trimethoprim, 97% of the parents reported giving antibiotics on daily basis, but in 31% of subjects, trimethoprim was not detectable in the urine.[6] Risk of prophylaxis includes nausea, vomiting, and rash in 8% to 10% of patients; development of resistant organisms; and change in indigenous microflora.[6] One study of resistance found that children who received antibiotics for more than 4 weeks in the previous 6 months were more likely to have resistant *Escherichia coli* isolates than children who had not received prolonged antibiotic treatment (odds ratio [OR]=13.9; 95% CI, 8.2–23.5). Children with abnormalities of the genitourinary tract were approximately 4 times more likely to have resistant isolates of *E coli* than children without abnormalities of the genitourinary tract (OR=3.9; 95% CI, 2.7–5.7).[11]

RECOMMENDATIONS FROM OTHERS

The American Academy of Pediatrics, American Urological Association, and the Swedish Medical Research Council guidelines recommend prophylaxis for children with reflux (**Table**), but they all acknowledge that the recommendations are not supported by well-designed randomized controlled trials.[1–3] No guidelines are available for children with neurogenic bladder and recurrent urinary tract infections.[7]

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TABLE

Oral antibiotics for prophylaxis of urinary tract infections in children

Antimicrobial	Prophylaxis dosage
Trimethoprim/sulfamethoxazole (TMP/SMX) (Bactrim, Septra)	2 mg of TMP, 10 mg of SMX per kg as single bedtime *or* 5 mg of TMP, 25 mg of SMX per kg twice per week
Nitrofurantoin (Macrodantin)	1–2 mg/kg as single daily dose
Cephalexin (Keflex)	10 mg/kg as single daily dose
Amoxicillin	10 mg/kg as single daily dose
Sulfisoxazole (Gantrisin Pedatric)	10–20 mg/kg divided every 12 h

Modified with permission from AAP 1999;[3] Allen et al1999.[10]

CLINICAL COMMENTARY:

UTI prevention most successful when the child exhibits efficiency of voiding

The relative benefit of antibiotic prophylaxis in prevention of UTI in children with anatomic abnormalities like vesicoureteral reflux could best be determined if all other risk factors for UTI were controlled. Unfortunately, these other factors are often more significant in promoting UTI than is reflux, and they are also more difficult to quantify. Voiding dysfunction and constipation can both increase bladder storage pressures and postvoid residual urine volumes, and as such greatly predispose children for UTI. Furthermore, a distended colon provides an abundant reservoir of pathogens with an array of uropathogenic virulence factors.

Published reports have failed to detect significant benefit for antibiotic prophylaxis in part because the children studied possess varying risks for UTI. Prevention of UTI is most successful when the child exhibits efficiency of voiding and elimination. Clinical practice in pediatric urology advocates use of antibiotic prophylaxis in children with vesicoureteral reflux. Reflux should be suspected in children with hydroureter, multicystic renal dysplasia, ureteral duplication, and ureterocele.

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Do acetaminophen and an NSAID combined relieve osteoarthritis pain better than either alone?

EVIDENCE-BASED ANSWER

Combining nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen for short courses provides more relief of pain in osteoarthritis without an increase in side effects (strength of recommendation [SOR]=**B**). Combining acetaminophen at 4 g/d with an NSAID can also decrease the daily dose of NSAID required for pain relief, thus reducing the potential risk from higher-dose NSAID therapy (SOR=**B**).

Over the long term, however, this combination may increase the risk of upper gastrointestinal (GI) bleeding more than that conferred by the NSAID alone (SOR=**B**). If combination therapy is necessary, limiting the dose of acetaminophen to ≤2 g/d minimizes gastrointestinal toxicity. Acetaminophen alone at the lowest dose to provide pain relief is the safest pharmacologic choice for patients with osteoarthritis.

EVIDENCE SUMMARY

Clinical guidelines for osteoarthritis recommend acetaminophen as first-line therapy followed by an NSAID or cyclooxygenase-2 (COX-2) inhibitor, and many patients are treated with combination therapy.

Several small randomized controlled trials have compared the individual efficacy of NSAIDs and acetaminophen in osteoarthritis and have found that both provide more pain relief than placebo.[1–3] There is a trend toward improved pain relief with NSAIDs compared with acetaminophen in the initial treatment period; however, few long-term studies of efficacy have been reported. One randomized controlled trial comparing 750 mg/d naproxen (Aleve, Naprosyn) with 2600 mg/d acetaminophen for 2 years found similar pain relief for both medications and a dropout rate of 65% in both groups.[2] Similar numbers of persons taking acetaminophen or naproxen dropped out because of adverse effects (20%) or lack of efficacy (19%), and no difference was seen in functional improvement between the 2 groups.

A 6-week randomized double-blind crossover trial of 227 patients comparing 75 mg diclofenac and 200 mg misoprostol (Arthrotec) with acetaminophen 4 g/d found the diclofenac-misoprostol combination provided more pain control than acetaminophen alone. Adverse events were slightly more common in the diclofenac group (54% vs 46%; P=.046).[4]

The COX-2 inhibitors rofecoxib (Vioxx) and celecoxib (Celebrex) have been shown to provide equal pain relief compared with naproxen for patients with osteoarthritis.[5] One industry-sponsored randomized trial found rofecoxib superior to celecoxib, and both superior to acetaminophen in treatment of osteoarthritis pain.[6] There was no difference in the incidence of side effects among the 3 medications. Thirty percent of patients taking 4 g/d acetaminophen discontinued the study because of lack of efficacy, compared with 20% of those taking either celecoxib or rofecoxib.[6]

Few studies have evaluated the safety or efficacy of the combination of NSAIDs and acetaminophen in osteoarthritis. One double-blind, double-dummy crossover trial of 18 patients with osteoarthritis of the hip compared naproxen at doses of 500 mg and 1000 mg, with and without 4 g/d of acetaminophen, and 1500 mg/d of naproxen alone over 5 one-week trial periods.[7] Adding acetaminophen improved patient-reported pain scores compared with naproxen alone. Higher doses of naproxen alone provided less pain relief than a lower dose of naproxen combined with acetaminophen. GI side effects increased with the increase in naproxen dose, but were unaffected by the addition of acetaminophen. Functional ability was not affected during this short study. A similar study by the same researchers of patients with rheumatoid arthritis found similar results.[7]

One randomized, double-blind, crossover trial compared single doses of tolmetin (Tolectin, 100,

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150, 200 mg) and acetaminophen (400 mg) alone and in combination with placebo in the control of experimentally induced pain (thermal and electrical stimulation). Acetaminophen alone did not differ from placebo in pain control; however, the combinations of acetaminophen with tolmetin provided similar pain relief to higher doses of tolmetin alone.[8] No studies have evaluated the efficacy or safety of acetaminophen combined with rofecoxib or celecoxib.

Regarding the risks of combining acetaminophen with NSAIDs, 1 nested case-control study based on the entire enrollment panel of the British National Health Service characterized the risk of upper GI side effects among persons taking NSAIDs or acetaminophen alone or in combination. The study evaluated medications in use at the time of an upper GI bleed, controlling for age, sex, and concomitant medications (corticosteroids, H_2 receptor antagonists, omeprazole, anticoagulants, and others) and excluding patients with varices, alcohol-related disorders, liver disease, and cancer; no attempt was made to control other comorbidities. The relative risk of upper GI perforation or bleeding for patients taking ≥2g/d acetaminophen or high-dose NSAIDs was 2.4 (95% confidence interval [CI], 1.7–3.5) and 3.6 (95% CI, 2.9–4.3), respectively. Concomitant use of an NSAID with ≥2 g/d of acetaminophen showed a relative risk of upper GI perforation or bleed of 16.6 (95% CI, 11.0–24.9). Acetaminophen doses <2 g/d conferred no additional risk for serious upper GI side effects.[9]

A systematic review of selective COX-2 inhibitors vs naproxen found fewer endoscopically detected ulcers in patients taking celecoxib but no difference in serious gastrointestinal bleeds.[5] A meta-analysis of randomized controlled trials found a higher incidence of serious thrombotic cardiovascular events among patients taking COX-2 inhibitors compared with naprosyn.[10] The safety profile of rofecoxib and celecoxib in the long-term treatment of pain is not fully understood at this time.

RECOMMENDATIONS FROM OTHERS

The American College of Rheumatology (ACR) recommends acetaminophen up to 4 g/d as a first-line pharmacologic treatment for osteoarthritis of the hip and knee, and advises NSAIDs be used at the lowest effective dose if they are necessary for pain control.[11] The ACR does not specifically comment on combining NSAID and acetaminophen use.

The American Academy of Orthopaedic Surgeons recommends initial use of an NSAID or acetaminophen, but does not comment on the combination of NSAIDs and acetaminophen.[12]

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CLINICAL COMMENTARY:

Adding acetaminophen may be more desirable than switching NSAIDs

Compared with NSAIDs, acetaminophen has a complementary analgesic mechanism of action and can be safely used in many patients. Additive effects of acetaminophen have not been well described with all NSAIDs (eg, COX-2 inhibitors); however, this combination is inexpensive and overall appears to effectively augment analgesia when combined with NSAIDs. Although observational data demonstrate an increased risk of upper GI bleeding with this combination, selection bias (higher-risk patients being on combination therapy) could reasonably explain this association. Adding acetaminophen may be more desirable than switching NSAIDs for patients with osteoarthritis that have a partial response to their current NSAID therapy.

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DRUG BRAND NAMES

Amoxicillin • Amoxil, Biomox, Polymox, Trimox, Wymox
Cephalexin • Biocef, Keflex
Celecoxib • Celebrex
Diclofenac/Misoprostol • Arthrotec
Ipratropium • Atrovent
Labetalol • Trandate
Methyldopa • Aldomet
Naproxen • Aleve, Anaprox, Naprosyn
Nitrofurantoin • Furadantin, Macrobid, Macrodantin
Rofecoxib • Vioxx
Tiotropium • Spiriva
Tolmetin • Tolectin
Triamcinalone • Aristocort, Atolone, Kenacort
Sulfamethoxazole/Trimethoprim • Bactrim, Cotrim, Septra, Sulfatrim
Sulfisoxazole • Gantrisin