Complementary and alternative medicine for upper-respiratory-tract infection in children

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Purpose. Evidence on the efficacy and safety of complementary and alternative medicine (CAM) for the prevention and treatment of upper-respiratory-tract infection (URTI) in children is reviewed.

Summary. A search of the literature to June 2005 identified six clinical trials examining the use of herbal medicines and nine trials of other CAM therapies. All articles were critically evaluated for adherence to standards of efficacy and safety research. Echinacea did not reduce the duration and severity of URTI. Andrographis paniculata or echinacea decreased nasal secretions (p < 0.01) but not URTI symptoms. A combination of echinacea, propolis, and ascorbic acid decreased the number of URTI episodes, the duration of symptoms, and the number of days of illness (p < 0.001). Echinacea was associated with a higher frequency of rash compared with placebo (p = 0.008). Neither ascorbic acid nor homeopathy was effective. The efficacy of zinc was not clear, and zinc may be associated with adverse effects in children. Osteopathic manipulation decreased episodes of acute otitis media (p = 0.04) and the need for tympanostomy tube insertion (p = 0.03) in children with recurrent acute otitis media. Stress-management therapy reduced the duration of URTI compared with relaxation therapy with guided imagery or standard care (p < 0.05).

Conclusion. Current data are generally inadequate to support CAM for the prevention or treatment of URTI in children.

Index terms: Alternative medicine; Andrographis paniculata; Antiinfective agents; Ascorbic acid; Echinacea species; Homeopathy; Minerals; Otitis media; Pediatrics; Plants; Propolis; Respiratory-tract infections; Toxicity; Vitamins; Zinc

Upper-respiratory-tract infection (URTI) occurs commonly in childhood. On average, a healthy three-year-old child suffers from 6–10 colds per year. URTIs are usually mild, viral, and self-limiting; however, the symptoms can cause fever and make children irritable, lethargic, and uncomfortable. The treatment strategy is to minimize symptoms and discomfort. Although widely used, nonprescription cough and cold preparations may not be effective for symptom control or shortening the illness. They may cause a wide variety of adverse effects, including paradoxical reactions and toxicity with unintentional overdosage, particularly in children less than three years old.

Complementary and alternative medicine (CAM) has been defined as “interventions neither taught widely in medical schools nor generally available in U.S. hospitals.” They are also referred to as nonallopathic, unconventional, holistic, or natural therapy. The Cochrane Collaboration defines CAM as “a broad domain of healing resources that encompasses all health systems, modalities and practices and their accompanying theories and beliefs, other than those intrinsic to the politically dominant health systems in a particular society or culture in a given historical period.” Generally, CAM products are used either in addition to or as a replacement of traditional Western medical or surgical treatment. CAM products include herbs, acupuncture, chiropractic spinal manipulation, homeopathy, relaxation techniques, diet, hypnosis, and spiritual healing.

In the United States, herbal products are not regulated by the Food and Drug Administration (FDA) as medicines and are considered dietary supplements. Thus, they do not nec-
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The purpose of this article is to review the evidence on the efficacy and safety of CAM for the prevention and treatment of URTI in children.

**Literature search**

A search was performed of MEDLINE (1966 to June 2005), EMBASE (1980 to June 2005), the Cochrane Database of Systematic Reviews (second quarter 2005), CAB International Abstracts (1972 to June 2005), International Pharmaceutical Abstracts (1970 to June 2005), and Alt-Health Watch (1990 to June 2005). The search terms included “children,” “pediatric,” “upper-respiratory tract infection,” “otitis media,” “sinusitis,” “pharyngitis,” “bronchitis,” “complementary and alternative medicine,” “homeopathy,” “spinal manipulation,” “acupuncture,” and “herbal.” The search was limited to human and clinical trials reported in English. A manual search of the references cited in various articles was also performed. Studies that included both adult and pediatric subjects but did not involve subgroup analysis by age group were excluded.

**Herbal medicine**

**Echinacea.** Echinacea (Echinacea purpurea) is a commonly used herb thought to prevent and treat common colds by stimulating the immune system. The evidence of efficacy in adults is conflicting. In a randomized, double-blind, parallel-group study of echinacea’s efficacy and safety in 407 children (mean ± S.D. age, 5.6 ± 2.9 and 5.4 ± 2.5 years in the echinacea and placebo groups, respectively) with 707 URTIs, investigators found no benefit in duration and severity of symptoms and an increased rate of rash in the echinacea group compared with placebo (7.1% versus 2.7%, p = 0.008). Pediatric dosing guidelines (in milligrams per kilogram) for echinacea do not currently exist. However, dosage in the study was based on age range and extrapolated from the adult dosage.

The pharmacokinetics of echinacea in children are also unclear. Thus, echinacea may have been ineffective in part because of a subtherapeutic dosage. A different species of echinacea (Echinacea angustiflora or Echinacea pallida) may have had different effects.

The age ranges on which the dosage was based may have led to large variations in the milligram-per-kilogram dosage between patients at the upper and lower limits of each range. Furthermore, a volume-based dosage (7.5 mL/day for patients 2–5 years old and 10 mL/day for patients 6–11 years old) of echinacea was used. The milligrams of echinacea per milliliter were not reported.

A randomized, double-blind, multicenter study examined the use of a herbal preparation containing echinacea 50 mg/mL, propolis 50 mg/mL, and ascorbic acid 10 mg/mL (Chizukit, Hadas Corp. Ltd., Yokneam, Israel) in 430 children one to five years old. Propolis, also known as bee glue, is a resinous substance collected by bees from a variety of plants to build and maintain hives. Children ages one to three years received 5 mL twice daily, and those ages four to five years received 7.5 mL twice daily. Mean ± S.D. age was 38.3 ± 18.6 and 38.9 ± 20.6 months in the Chizukit and placebo groups, respectively. Propolis is thought to have antimicrobial activity, anticancerous properties, antiinflammatory effects, and antiviral effects. Twenty-three percent of the participants dropped out of the study within the first week, most commonly because of the unpalatability of both the herbal and placebo preparations. Study enrollment was adjusted to allow a 50% dropout rate; therefore, power was maintained. The authors concluded that the herbal preparation decreased the rate of URTI, including acute otitis media, tonsillopharyngitis, and pneumonia. They also found a decrease in the total number of days of fever, antipyretic...
use, antibiotic use, unscheduled visits to the physician, and absence from daycare or kindergarten in the herbal preparation group ($p < 0.001$). Adverse drug reactions were reported as mild transient gastrointestinal and palatability symptoms and were similar in the treatment and placebo groups. Rash was not reported.

Spasov et al.\textsuperscript{24} conducted a three-group study in 133 children (mean ± S.D. age, 6.89 ± 0.18 years) comparing echinacea, \textit{Andrographis paniculata} (kan jang), and standard treatment. \textit{A. paniculata} is a herb believed to reduce symptoms of common colds and viral URTI. Standard treatment for the control group consisted of “lavish” warm drinks, throat gargles with matricaria (chamomile) infusion, antiseptic nose drops of silver nitrate colloid p.r.n., and acetaminophen 500 mg three times daily if fever or severe headache was present. Typical administration of acetaminophen on a milligram-per-kilogram basis was not used. The standard treatment did not reflect typical treatment of children with a cold in North America.

The \textit{A. paniculata} was administered as two tablets three times daily for 10 days (30 mg of andrographolide and deoxyandrographolide per day), which was in accord with the dosage recommendations of the Swedish Herbal Institute. The echinacea group received 10 drops three times daily for 10 days. Echinacea administration was expressed as milligrams of echinacea pressed juice per 100 mL of oral solution; the milligram dosage was not reported. The echinacea product contained 20% alcohol.

An improvement in URTI symptoms by days 2–3 was reported in all groups. The authors reported a faster improvement in symptoms in the \textit{A. paniculata} group ($p < 0.002$) and a decrease in nasal secretions in the \textit{A. paniculata} and echinacea groups compared with the standard treatment on day 5 ($p < 0.01$) of five drops to the affected ear canal of either.

**Herbal ear drops.** Herbal ear drops (Otitonik solution, Healthy-On Ltd., Petach-Tikva, Israel, containing \textit{Allium sativum} [garlic], \textit{Verbascum thapsus} [a homeopathic remedy], \textit{Calendula flores} [marigold], and \textit{Hypericum perforatum} [St. John’s Wort] in olive oil) were compared with anesthetic ear drops (Vitamed Pharmaceutical Ltd., Benyamina, Israel, containing ametocaine and phenazone in glycerin) for the relief of pain from acute otitis media in a randomized, double-blind trial enrolling 110 children (median age, 8.1 years for girls and 8.3 years for boys).\textsuperscript{20} Pain was measured on a 10-point Likert scale, with 1 representing no pain and 10 the worst pain possible; a facial pain scale; and a color pain scale. The groups were unbalanced with regard to bilateral acute otitis media: 28 children (77.8%) in the herbal-ear-drop group and 8 children (22.2%) in the anesthetic-ear-drop group had bilateral infection.

Reduction in pain by day 3 was seen in both groups. The difference in mean pain levels between the two groups was also similar. The only significant difference was the mean pain score on day 1 at 30 minutes after administration. The herbal-ear-drop group had less pain (mean pain score, 3.1, versus 4.3 in the anesthetic-ear-drop group; $p = 0.07$). Children in the study also received acetaminophen, so pain reduction may be attributed at least in part to acetaminophen and not ear drops. The authors concluded that the two drop preparations were equivalent; however, no power or sample-size analysis was provided to interpret the data clearly.

A four-group study comparing naturopathic herbal extract ear drops (NHED, M. Pharm Co., Petah Tiqwa, Israel), NHED plus high-dose amoxicillin (80 mg [as the trihydrate]/kg/day divided three times daily), anesthetic otologic drops, and anesthetic otologic drops plus high-dose amoxicillin for the treatment of ear pain secondary to acute otitis media was performed in 180 children (mean ± S.D. age, 6.81 ± 3.88 years).\textsuperscript{26} NHED contained \textit{A. sativum}, \textit{V. thapsus}, \textit{C. flores}, \textit{H. perforatum}, lavender, and vitamin E in an olive oil base. All four treatment groups had a decrease in ear pain within 15 minutes of initial administration and a 77.8–95.9% decrease in pain over three days, with mean pain scores decreasing from ranges of 7.8–9.1 to 0.3–2.0 (no $p$ values provided). Concomitant antibiotic treatment did not affect outcomes. No comparison with placebo was made, so pain may have been self-limited. No adverse reactions were documented. These data suggest that otologic drops (either herbal or anesthetic) may decrease ear pain in children with acute otitis media during the first three days, even if antibiotics are not administered. It is unknown whether the drops would have a benefit over watchful waiting or acetaminophen.

**Chinese herbal medicines.** Allergina, a traditional Oriental medicine and a herbal combination medication used in Asia to enhance immune response and inhibit allergic inflammation,\textsuperscript{27} was studied for the treatment of otitis media with effusion.\textsuperscript{28} Allergina contained a decoction of \textit{Schizonepetae herba}, \textit{Forsythiae fructus}, \textit{Ledebouriellae radix}, \textit{Angelicae radix}, \textit{Cnidii rhizome}, \textit{Paeoniae radix alba}, \textit{Angelicae dahuricae radix}, \textit{Bupleuri radix}, \textit{Auravitini fructus}, \textit{Scutellariae radix}, \textit{Fructus angelicae}, \textit{Platycodi radix}, \textit{Glycyrrhizae radix}, \textit{Trichosanthis radix}, \textit{Taraxaci herba}, and \textit{Lonicerae flos}.

Allergina was compared in a prospective, parallel-group trial with unspecifed antibiotics for symptom resolution and effects on immune mediators and interleukin (IL) levels in 17 children (mean age not reported) with otitis media with effusion.\textsuperscript{28} The IL-2 and IL-4 levels were significantly higher in the allergina treat-
ment group, and clinical signs of otitis media with effusion were greatly diminished after patients received allergina. The method of treatment allocation, power and sample-size calculations, outcome measures for clinical signs of otitis media, and criteria for evaluating treatment success were not stated. Thus, the efficacy and safety of allergina in the management of otitis media with effusion are unclear.

Liu and Douglas published a review of Chinese herbal medicines for the treatment of URTI. Twenty-six of the 27 studies reviewed were published in Chinese, and only 1 was in English (and it involved adult patients). Although a majority of the studies found Chinese herbal medicines to be superior to antibiotics for the treatment of URTI, the quality of the studies was generally poor. Therefore, no conclusions could be made about efficacy and safety.

**Ascorbic acid**

Two randomized, double-blind studies conducted in Navajo schoolchildren (mean age not reported) found no difference among ascorbic acid 1000 mg/day, ascorbic acid 2000 mg/day, and placebo in number of URTI episodes or illness duration. An analysis of the mean duration of URTI episodes and plasma ascorbic acid concentrations (grouped as low, middle, and high—absolute values not reported) demonstrated a longer mean duration in the high-concentration group compared with the middle-level and low-level groups ($p < 0.05$).

A randomized, double-blind study of ascorbic acid 500–1000 mg/day (weight-based dosages, weight ranges not specified) for the prevention of URTI in 88 children (44 pairs of twins ages 6–15 years) found no difference between treatment and placebo in prevention or treatment effects. However, some subgroups, younger children receiving 500 mg/day and girls in the two youngest age groups, had shorter and less severe episodes. The study did not have adequate power to determine whether this finding was an ascorbic acid effect or a confounding effect of genetic, environmental, or other nature. There is no substantial evidence to support the use of megadosages of ascorbic acid ($\geq 1000$ mg/day in older children, or $\geq 500$ mg/day in younger children) for preventing URTI episodes or decreasing their severity or duration in children.

**Cod liver oil**

Linday et al. discovered that children with recurrent otitis media had low red-blood-cell concentrations of the omega-3 fatty acid eicosapentaenoic acid (EPA), vitamin A, and selenium compared with either children without recurring otitis media or adults. Thus, an open-label clinical trial examined the use of cod liver oil with selenium containing multivitamins for the secondary prophylaxis of otitis media. Recommended daily allowances for omega-3 fatty acids have not been established for children.

The investigators used lemon-flavored cod liver oil (J. R. Carlson Laboratories, Arlington Heights, IL) (5 mL/day, containing the equivalent of 45–50 mg of $\alpha$-linolenic acid, 460–500 mg of EPA, 500–550 mg of docosahexaenoic acid [omega-3 fatty acids], 2000–2500 IU of vitamin A, 400–500 IU of vitamin D, and 1 IU of vitamin E). The multivitamin product selected was Carlson’s Scooter Rabbit chewable vitamins and minerals (one-half tablet per day, containing vitamin A 2500 IU, vitamin D 200 IU, vitamin E 30 IU, vitamin K 20 μg, ascorbic acid 60 mg, thiamine 0.75 mg, riboflavin 0.85 mg, niacin 2.5 mg, pyridoxine hydrochloride 1.0 mg, folate 100 μg, cyanocobalamin 3 μg, biotin 15 μg, pantothenic acid 5 mg, calcium 25 mg, iron 4.5 mg, phosphorus 11 mg, iodine 37.5 μg, magnesium 12.5 mg, zinc 3.75 mg, selenium 17.5 μg, copper 0.5 mg, manganese 0.88 mg, chromium 30 μg, molybdenum 19 μg, and potassium 1.25 mg).

The endpoints were the percentage of days of antibiotic therapy before and during cod liver oil treatment. “Before treatment” was defined as the period from September 1, 2000, to the date of study enrollment (December 2000–January 2001). “During treatment” was defined as the date of enrollment through the end of the study (March 31, 2001). Enrollment occurred over a three-week period. Five of the seven children (mean ± S.D. age, 3.8 ± 1.8 years) who completed the trial were considered responders (no cases of otitis media during the study period). All five children had at least one URTI during the study period, but it resolved without additional treatment. The suboptimal study design and small sample size make any definitive conclusions impossible.

**Zinc**

It has been suggested that zinc deficiency may affect the susceptibility of children and adults to colds. Mackin et al. performed a randomized, double-blind, placebo-controlled trial to determine the efficacy of zinc gluconate glycine lozenges against colds in 249 children and adolescents (ages 6–16 years). There was no difference in time to resolution of cold symptoms between the zinc and placebo groups. Although the overall difference in reported adverse effects was not significant, bad taste, nausea, oral discomfort, and diarrhea occurred more frequently with zinc than with placebo ($p < 0.05$).

The effectiveness of zinc gluconate glycine lozenges for preventing colds in 382 adolescents living in a monitoring and rehabilitation facility for adolescents with mental illness, substance abuse, and behavioral problems was studied retrospectively. The frequency of colds and the duration of symptoms in the residents liv-
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Zinc lozenges in reducing the occurrence and the effectiveness of prophylactic treatment group. The duration and severity of colds were diminished in the prophylactic group compared to the no-prophylaxis group. The same facility to evaluate the effectiveness of homeopathic treatment with placebo for acute otitis media was conducted in 75 children (mean ± S.D. age, 42.1 ± 15.9 years and 3.6 ± 13.6 months in the homeopathy and placebo groups, respectively). The goal of the study was to determine clinical response and the sample size required for a future trial with adequate power. Several homeopathic medicines were used, depending on the child’s initial symptoms. The study found no difference between the treatment (most commonly chamomilla, sulfur, Pulsatilla nigrans, or calcium carbonate three to five pellets sublingually three times daily for five days or until improvement) and placebo groups in treatment failures (defined as ear pain or fever of >38 °C [measured orally] during the first 48 hours of treatment or severe ear pain resulting in crying or fever of >39 °C after the first 24 hours) at five days, two weeks, and six weeks. There was no difference in the presence of middle-ear effusion at two and six weeks.

Although there was a difference in symptom scores over the first 72 hours, the authors calculated that 243 children would be needed in each group to detect a significant difference between the groups with α = 0.05 and a power of 80%. No adverse drug reactions were reported in either group.

The efficacy, safety, and cost-effectiveness of homeopathy for acute otitis media were assessed in 230 children (mean age not reported) coming to a clinic for treatment. The patients received 1 of 26 homeopathic medicines chosen on the basis of their symptoms. The authors did not state the methods used to assess pain. An antibiotic was given if the child still had pain 12 hours after the first dose and 6 hours after a second dose. Whether analgesics were given was not stated. No conclusions can be made.

A comparison of individualized therapy with homeopathy medicines (based on symptoms) versus placebo in 75 children (median age, 4.2 years [range, 1.5–9.8] years and 3.6 [1.7–7.9] years in the homeopathy and placebo groups, respectively) with recurrent URTI showed no difference in daily symptom scores, the number of antibiotic courses, or the proportion of children having adenoidectomies or tonsillectomies. No information regarding adverse reactions was reported.

Physical manipulation

A pilot study attempted to examine the feasibility of comparing chiropractic spinal manipulation with sham or placebo spinal manipulation for chronic otitis media with effusion in children (median age, 1.9 years). The investigators initially sought to collect data on middle-ear effusion improvement via tympanometric and otoscopic examinations and on the number of parent-reported days of clinical symptoms of otitis media. However, difficulty in examining patients (during 25% of visits, the child cried or was so active that tympanometric and otoscopic data could not be obtained) and the small number of patients enrolled precluded any conclusions.

Osteopathic manipulation (total of nine visits) as an adjunct to antibiotics was compared with routine care in children with recurrent acute otitis media was studied in 57 patients. Nineteen children (6 intervention-group patients and 13 control patients) dropped out during the study.
because of loss of continuity of care or the inconvenience of a six-month study. Sixty-eight percent of the children were under two years of age (mean ± S.D. age, 2.6 ± 20.29 months in the intervention group and 19.88 ± 13.18 months in the control group). The osteopathic manipulation (intervention) group had fewer episodes of acute otitis media (p = 0.04) and fewer tympanostomy tube insertions than the control group (p = 0.03). The numbers of antibiotic courses were similar in the two groups.

**Psychological therapy**

Similar to findings in adults, an association between psychological stress and susceptibility to URTI has been found in children.43 The effects of stress-management therapy were compared with those of relaxation therapy with guided imagery and a control condition (a waiting list for therapy) in 45 children (mean age, 9.4 years) with recurrent URTI.44 Stress management involved relaxation procedures, distraction techniques, and methods to improve coping. In the relaxation therapy group, children mentally pictured a favorite place, imagined their body and immune system clearing away germs, practiced relaxed breathing, and listened to a relaxation tape. Endpoints were the frequency and duration of URTI, mucosal immunity, and immunoglobulin A (IgA) concentrations. Recurrent URTI was defined as 10 or more URTI episodes in the previous year. Outcomes were measured from child-reported (under parental supervision) daily symptom diaries recorded each evening. A symptomatic episode of URTI was defined as the presence of two or more symptoms for ≥24 hours or one symptom for ≥48 hours (when parents thought that their child had an URTI and not an allergy). Episodes were separated by at least three days of no symptoms. Secretory IgA was measured in saliva at baseline (when the child had been symptom free for 2 weeks) and weekly during the 13-week study. Samples taken from children with URTI were excluded. Personality and mood profiles were also reported. One child in each group withdrew prior to completing the trial.

The frequency of URTI episodes was similar among all three groups, but the duration of symptoms was significantly shorter in the psychological treatment groups than in the control group (p < 0.001) and in the stress-management-reduction group than in the group receiving relaxation therapy with guided imagery and the control group (p < 0.05). Levels of secretory IgA were similar among groups. Thus, stress-management therapy may decrease the duration of URTI symptoms in children with recurrent URTI.

**Discussion**

Poor study design, small sample size, and inadequate or unknown power within a majority of the trials make it difficult to formulate conclusions regarding the efficacy and safety of various CAM therapies for URTI in children. Although most pediatric CAM users are children with chronic disease, the studies were done in otherwise healthy children with URTI who were not taking any medications. Thus, the data may not be generalizable to the chronically ill population or to children taking medications for extended periods. Preparations studied often included several herbs or CAM products, making it difficult to determine which active ingredients were contributing to efficacy or adverse events.

In many trials involving oral administration of CAM products, the dosages were extrapolated from adult dosages and did not involve typical weight-based (milligram-per-kilogram) dosages used in pediatrics. It is unknown if this led to a large variation in serum concentrations of active constituent among subjects and thus affected efficacy or safety.

The currently available data do not support the use of CAM for the prevention or treatment of URTI in children. There are conflicting data regarding the efficacy and safety of echinacea. The trial with positive efficacy results on reducing the number of episodes and the duration of symptoms used a herbal product with echinacea in combination with propolis and ascorbic acid, whereas the trial with echinacea alone showed no efficacy and increased rash. The efficacy of ascorbic acid alone or homoeopathy has not been proven. Zinc lozenges may not be effective and may cause some adverse effects in children and adolescents. While CAM may be viewed as a potential alternative or complement to traditional drug therapy, including antibiotics, it is important to recognize the potential adverse effects (such as rash with echinacea) and the fact that most URTIs are viral and resolve without treatment.

Limited data suggest that stress-management psychotherapy may decrease symptom duration and play a role in the management of recurrent URTI in children. One study found that osteopathic manipulation as an adjunct to antibiotic therapy may decrease the frequency of episodes of acute otitis media in children less than six years of age with recurrent otitis media.

Large, randomized, controlled trials with adequate sample sizes and power are required before conclusions can be made about the efficacy and safety of various CAM products for preventing or treating URTI in children.

**Conclusion**

Current data are generally inadequate to support CAM for the prevention or treatment of URTI in children.