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Complementary and Alternative Medicine Therapies for Cold and Flu Season: What Is the Science?

Kathi J. Kemper, MD, MPH

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The Cases

Jessica is a 37-year-old married mother of 2 boys -- one in prekindergarten and the other in second grade. She would like to reduce her family's risk of getting H1N1 influenza this year. Jessica understands the importance of hand washing, covering sneezes and coughs, and avoiding contact with ill people. She has been advised to get a flu vaccine, but also wants to know whether any vitamins, minerals, or homeopathic remedies can protect against influenza. Jessica is already making sure her boys get "plenty of fluids" and "plenty of sleep."

David is a volunteer firefighter and emergency medical technician who has irritable bowel syndrome (IBS). After a nurse told him that probiotics might help his IBS symptoms, David looked up probiotics on the Internet and learned that they might promote optimal immune function. David asks whether taking probiotics can help prevent respiratory infections this winter.

Laura is a competitive ice skater who wants to know what kind of herbal cold and flu remedies are appropriate to use according to the International Olympic Committee (IOC). Her grandmother gives her tea with honey and lemon when she gets a scratchy throat and cough. Jessica's mother cooks with extra garlic and makes a big batch of her chicken soup as soon as the first person in the family starts coughing in November. Jessica's friend, Juan, says his grandmother tells him that to reduce his risk of catching a cold, he should not drink milk or eat cold foods. Laura is pretty sure all these remedies are acceptable to the IOC, but she wonders whether there are specific herbal products she can take if she starts to feel sick. She knows she can't take over-the-counter decongestants, and antihistamines make her feel too foggy to function.

Commentary

Influenza-like illnesses (ILI) and upper respiratory tract infections (URTI) typically peak in prevalence in the late fall through early spring. The media extol the benefits of good hygiene and immunizations, echoing the advice of healthcare professionals. In addition, home remedies and natural products have long been used to prevent and treat common viral illnesses. How should clinicians advise patients about the effectiveness and safety of these remedies when used to enhance immune function to prevent or treat virally mediated ILI or URTI?

Home Remedies

Home remedies range from diet (chicken soup or garlic) and dressing (warm head and feet) to poultices and vaporizers. Culturally, some families avoid cold foods (including dairy) and encourage spicy foods (such as garlic and ginger). Hot tea with honey and lemon is another popular remedy during winter months. Some mothers rub salves containing menthol, thyme, or eucalyptus on the sick family member's chest, and others make mustard poultices or enforce wearing hats, scarves, or warm socks. Hot steam or cool mist vaporizers are commonly used to increase household humidity and soothe dry respiratory passages; neti pots (small vessels with long narrow spouts) and saline rinses are used to wash viruses, allergens, and mucus out of the nose. Whether home remedies are effective prophylactic or therapeutic agents, or just make patients feel better to use them, these practices are generally safe and support cultural identity and self-efficacy, and their use can be tolerated by healthcare providers.[1]

Sleep and Fluids

"Drink plenty of fluids" is well-worn advice that may have a basis in its common sense consequences. Dehydration can dry the respiratory mucosal surfaces; however, there is little evidence that drowning in extra fluids improves resistance to viral infections. On the other hand, the frequent trips to the restroom necessitated by larger than usual intake of fluids may promote

additional hand washing, thereby reducing the spread of infections.

"Get plenty of sleep" is another adage voiced by grandmothers as well as clinicians, with the intent of supporting immune function. Sleep deprivation is associated with disruptions of immune function.[2] In laboratory studies, depriving healthy adults of sleep induces a significant increase in both pro-inflammatory and anti-inflammatory markers (ie, E-selectin, intracellular adhesion molecule-1, interleukin [IL]-1beta, and IL-1 receptor antagonist) and a significant decrease in C-reactive protein and IL-6.[3] Sleep deprivation can also impair the immune response to influenza vaccine. In a study of adult volunteers, influenza immunizations were administered to one group after 4 nights of partial sleep deprivation (sleep restricted to 4 hours per night) and to a second group after 4 full nights (7.5-8.5 hours per night) of sleep. Ten days after vaccination, mean antibody titers in the sleep-deprived volunteers were less than half of those in the volunteers who had normal sleep durations.[4] Because individuals with poorer responses to vaccines also experience higher rates of illness, these findings support the concept that adequate amounts of sleep are important for optimal immunity during respiratory illness seasons. There are no data to suggest that excessive sleep (more than 10-12 hours per night for adolescents and adults) further improves immune function, but it appears prudent to avoid sleep deficits.

Jessica is wise to ensure that those in her family practice good hygiene, maintain good hydration, avoid sleep deficit, and receive immunizations.

Natural Health Products

A growing number of randomized controlled trials have evaluated the effectiveness of natural health products. What is the scientific evidence for the effectiveness and safety of vitamin and mineral supplements, herbal products, or probiotics and homeopathic remedies in preventing or treating ILI and URTI?

Vitamins and Minerals

Vitamin C. Vitamin C (ascorbic acid) is the vitamin most often associated with warding off viral respiratory infections. A Cochrane systematic review of 30 randomized trials involving more than 11,000 adults concluded that prophylactic vitamin C supplementation (200 mg or more daily) is not effective in reducing the incidence of URTI in most adults (odds ratio 0.96; CI 0.92-1.0). On the other hand, a subgroup analysis of 642 very healthy adults engaged in highly physically stressful activities (marathon runners, skiers, and soldiers on subarctic exercises) showed a 50% decrease in the risk of developing a cold among those who took vitamin C supplements.[5] In the 30 studies that examined the impact of prophylactic vitamin C supplementation on the duration of URTI symptoms, vitamin C conferred a consistent benefit on reduction of cold duration (8% in adults and 14% in children). Of the 7 studies that assessed the impact of therapeutic vitamin C supplementation (taking vitamin C after symptoms had begun), there was no overall benefit on the severity or duration of URTI symptoms.

Vitamin C has mild in vitro antiviral activity against influenza virus,[6,7] and vitamin C deficiency impairs effective immune response to influenza viral infections in male mice.[8] However, clinical studies supporting the use of supplemental vitamin C to prevent or treat seasonal or atypical influenza are lacking.

Side effects of vitamin C (in daily doses exceeding 3 to 6 g) include diarrhea and upset stomach; otherwise, the side effect profile of vitamin C is similar to that of placebo. Vitamin C appears to be most useful as a prophylactic agent to reduce the duration of URTI symptoms in children and in healthy adults undergoing physical stress. It does not appear to be useful once symptoms have started, and there is insufficient evidence to recommend its use for prophylaxis or treatment of ILI.

Vitamin D. Despite widespread fortification of food with vitamin D and the use of multivitamins, suboptimal vitamin D levels are increasingly reported in adults and pediatric populations in North America, particularly among those who are overweight and those with darker skin pigmentation.[9,10] For example, according to the National Health and Nutrition Examination Survey (NHANES), the prevalence of optimal vitamin D levels (30 ng/mL or higher) in non-Hispanic blacks fell from 12% in 1988-1994 to 3% in 2001-2004.[11]

In addition to its well known effects on bone health, vitamin D is an important immune regulator, stimulating innate immunity and moderating inflammation. A secondary analysis of NHANES data from 1988-1994 showed an inverse relationship between vitamin D levels and incidence of URTI.[12] These results have been supported by other studies that show an increased risk

for severe acute lower respiratory illness in people with low vitamin D levels.[13,14] Historically, the association between rickets and risk for severe respiratory infection is well known,[15] and vitamin D deficiency is associated with an increased risk for influenza.[16,17]

Controlled trials of vitamin D supplementation, however, have had mixed results. In a randomized controlled trial of healthy adults with normal vitamin D levels, supplementation with 2000 IU of vitamin D daily had no significant impact on URTI incidence, duration, or severity.[18] In a controlled trial of vitamin D supplementation to decrease bone loss in black women, a secondary finding was a significant reduction in the incidence of URTI and ILI respiratory illnesses among the women receiving vitamin D supplementation, particularly during the winter months.[19]

In controlled trials, serious side effects from vitamin D supplements have been rare.[20] Given the historical and epidemiologic data, randomized controlled trials of vitamin D supplementation to prevent and treat URTI and influenza are urgently needed, and while results of such studies are pending, it is prudent to avoid vitamin D insufficiency.

Zinc. The essential mineral, zinc, plays an important role in immune function. Zinc is a structural component of many enzymes and serves as an intracellular signal between immune cells.[21] The activity of virtually all immune cells is modulated by zinc, and zinc deficiency leads to dysfunction of both humoral and cell-mediated immunity and increases susceptibility to infection.

Zinc deficiency is associated with an increased incidence and severity of pneumonia.[22] In developing countries, zinc supplementation has been shown to decrease the incidence of childhood pneumonia.[23] A meta-analysis of studies reported that zinc supplementation reduced the incidence of acute lower respiratory tract infections in children by approximately 15%.[24] The effectiveness of zinc supplements in preventing or treating influenza-like illnesses requires additional research in better nourished populations.

Studies of the effectiveness of zinc supplements in preventing or treating URTIs have had mixed results. In a 2009 study of healthy Air Force cadets, zinc supplementation (15 mg daily for 7 months) was not associated with a decrease in the incidence of upper respiratory illnesses.[25] Open-label studies of a zinc gluconate glycine lozenge (Cold-EEZE®) suggested a 25% reduction in the duration of cold symptoms in children who received the lozenge.[26] In a meta-analysis of 8 randomized, placebo-controlled trials of zinc supplementation in the treatment of recent-onset colds, 4 trials showed significant improvements, and the other 4 trials showed no improvement. The benefits of zinc supplementation were most apparent among those who began taking zinc shortly after symptoms began, and who used products that did not contain citric or tartaric acid.[27] A larger analysis of 14 controlled trials of zinc supplementation that were published from 1996 to 2006 suggested that zinc was not more effective than placebo as a remedy for colds.[28] A more recent randomized controlled trial in Turkish children who started zinc supplementation shortly after cold symptoms developed showed a significant decrease in symptom severity but not in symptom duration.[29] In another recent trial, adults were randomly assigned to zinc lozenges (13.3 mg of zinc acetate every 2-3 hours while awake) or placebo. The zinc group showed significant improvements in symptom severity and duration without significant adverse effects.[30]

Zinc gluconate glycine lozenges are generally safe and well tolerated, but they can cause a metallic taste, nausea, and upset stomach.[31] Because of the risk of choking, lozenges should not be given to young children. Nasal swabs and nasal sprays that contain zinc have led to anosmia (loss of sense of smell); these products should be avoided until further studies demonstrate safety.[32]

Homeopathic zinc products are extremely dilute preparations that are generally very safe; they are not the same as non-homeopathic (allopathic) zinc lozenges or nasal swabs. There are no published clinical trials evaluating the effectiveness of homeopathic zinc as a remedy for URTI or ILI.

Overall, in spite of inconsistent evidence, it seems prudent to avoid zinc deficiency, although zinc supplementation in healthy, well nourished populations does not appear to reduce the risk for upper respiratory infections. Data on the effectiveness of lozenges in reducing the duration and severity of established URTIs have been mixed. Although lozenges appear to be safe, zinc nasal gels and swabs have side effects. Homeopathic zinc preparations are also safe, but clinical trial evidence of a benefit in preventing or treating URTI or ILI is lacking.

Herbal Products

In traditional practice, herbs are used to treat symptoms or for short term systemic support (up to 8 weeks) during cold and flu season. Herbs such as echinacea are generally not taken for longer than 6-8 weeks. Ginseng may be used for longer periods by elderly or debilitated patients. Other natural products, such as garlic, elderberry juice or jam, and honey, are considered foods and may be taken daily for long periods of time as part of a normal diet.

Andrographis. *Andrographis paniculata* is a bitter herb used in ayurvedic medicine (traditional medicine from India). Although not as well known in the United States as other herbs, andrographis has support from several clinical trials as a therapy for URTI.[33] A review of 7 trials involving nearly 900 patients, including children, suggests that andrographis is significantly more effective than placebo in treating cold symptoms if started promptly (within 36-48 hours) after their onset.[34,35] Several studies with positive findings used a preparation that combines andrographis with eleutherococcus ginseng (Swedish Kan Jang).[36] Russian studies have favorably compared andrographis (using the Swedish Kan Jang preparation) to amantadine as a treatment for influenza infection.[37] Andrographis supplements are generally well tolerated, but anaphylaxis has occurred. Additional studies are needed to determine its effectiveness in preventing URTIs and preventing or treating ILI in diverse populations in North America.

Echinacea. Research generally supports the use of high quality *Echinacea purpurea* products by adults to prevent or treat URTI. A 2007 meta-analysis of 14 controlled trials in adults concluded that *E purpurea* taken prophylactically decreased the odds of the common cold developing by 58% and decreased the duration of a cold by 1.4 days (both statistically significant).[38] A 2006 Cochrane review evaluated studies of echinacea as a therapy for URTIs. Although most of the 16 studies that evaluated echinacea using aerial plant parts found that echinacea was more effective than placebo as a treatment for URTIs, it was suggested that additional rigorous trials are needed.[39] A large controlled trial in pediatric patients found that echinacea may help prevent pediatric colds when taken during cold and flu season[40]; however, echinacea does not seem to reduce the duration or severity of symptoms when used to treat colds in children.[41]

In vitro, echinacea inhibits the production of pro-inflammatory cytokines induced by the influenza virus and shows direct antiviral activity.[42] Additional research to explore the clinical significance of this observation in preventing or treating ILI is needed. In most studies, echinacea has been well tolerated, but allergies and skin rashes are possible. There is substantial variability in echinacea products sold in the United States. Most of the studies that showed positive results used Echinacea Madaus (Madaus GmbH, Köln, Germany), which uses aerial portions of the *E purpurea* species.

Elderberry. European black elderberry (*Sambucus nigra*) juice, (marketed as the extract Sambucol® [PharmaCare US, San Diego, CA]) is widely used to treat URTI and ILI. In vitro, elderberry binds to and prevents infection with influenza H1N1 virus.[43] Studies from Israel and Norway suggest that black elderberry extract (1-4 tablespoons daily for 3-5 days for adults) can inhibit the growth of influenza viruses in vitro and shorten the duration of influenza symptoms while enhancing antibody levels against the virus.[44-46] However, additional studies are needed to confirm these effects in more diverse North American populations (including children) before elderberry becomes a routine recommendation for preventing or treating ILI.[47] No studies have demonstrated effectiveness of elderberry extracts in preventing or treating URTI. Elderberry is generally well tolerated, although allergic reactions are possible.

Garlic. Garlic (*Allium sativum*) is a commonly used food and folk remedy for preventing and treating the common cold. One high-quality trial of the effect of garlic supplementation on the common cold found that a daily garlic supplement (180 mg allicin content for 12 weeks) significantly reduced the incidence of the common cold.[48] Randomized clinical trials have not addressed the effectiveness of garlic in treating URTIs or in the prevention or treatment of influenza. Garlic is generally safe, but its unpleasant effects on breath, belching, and body odor are well known.

Ginseng. Randomized clinical trials suggest that prophylactic standardized North American ginseng (*Panax quinquefolium*) supplements (COLD-fx®, Afexa Life Sciences Inc., Edmonton, Alberta, Canada) taken daily for 4 months can significantly reduce the incidence (by approximately 25%) and duration (by approximately 6 days) of URTIs in adults.[49-51] In traditional herbal medicine, this herb is given to elderly or debilitated patients, not to healthy adults or children. COLD-fx® is marketed as a treatment for URTI, although randomized controlled trials have not evaluated its benefits as a treatment once symptoms have begun.[52] Additional research is needed to assess the effectiveness of ginseng in preventing and treating URTIs in pediatric patients.

A randomized controlled trial from Italy evaluated the benefits of a standardized product (Ginsana®, Alan James Group, Boca

Raton, FL) of a different ginseng species (*Panax ginseng*) as an adjunct to influenza immunization. Taking 100 mg of *P ginseng* daily for 4 weeks before and 8 weeks after influenza immunization was associated with significantly higher antibody levels and natural killer cell activity compared with taking placebo.[53] More research is needed to assess the safety and effectiveness of ginseng when used as a single agent to prevent or treat ILI in adult and pediatric patients.

Ginseng may cause hypertension and agitation in large doses but otherwise is generally safe.

COLD-fx® was chosen by the IOC as an official cold and flu remedy for the 2010 Winter Games.

Laura decided that because a ginseng supplement had been approved by the IOC, she would start taking ginseng supplements 3 weeks before her winter events to reduce her risk for a respiratory illness that could interfere with her skating.

Honey. Honey is a home remedy commonly used to treat the symptoms of respiratory infections, particularly scratchy throats and coughs. A randomized controlled trial of 105 children with colds supports the use of buckwheat honey to quiet coughs that interfere with sleep.[54] Honey has not undergone formal study to evaluate its prophylactic effects on the incidence of URTIs or in the prevention or treatment of ILI. Because of the risk for botulism, honey should not be given to children younger than 1 year old.

Pelargonium. African geranium (*Pelargonium sidoides*) is a native plant of South Africa used by Zulu and Basuto people. Two systematic reviews of 3 adult trials and 3 pediatric trials (most of which used the plant extract EPs 7630) concluded that pelargonium may be effective in alleviating symptoms of the common cold and bronchitis in adults.[55,56] The benefits of pelargonium in treating cold symptoms were confirmed in a randomized controlled trial published in 2007.[57] Additional research is needed to determine its effectiveness in preventing URTIs and in preventing or treating ILI in diverse populations. The product is well tolerated; side effects of the most common preparation (Zucol™, Abkit, Inc., New York, NY) include allergic reactions and upset stomach.

Probiotics

Probiotics encompass a large heterogenous group of bacteria that are normal inhabitants of the human gastrointestinal tract. These live microorganisms have undergone intensive study as treatments for gastrointestinal problems such as diarrhea, constipation, and IBS and as therapy for atopic conditions. Recently, research has focused on the potential role of probiotics in preventing respiratory illnesses in adults and children. For example, in a controlled study in 10 healthy adults, taking 1 daily capsule of *Bacillus coagulens*, a patented probiotic (GanedenBC30, marketed as Sustenex™, Ganeden Biotech, Inc., Mayfield Heights, OH), for 30 days significantly increased T-cell production of tumor-necrosis factor-alpha in response to exposure to adenovirus and influenza A (H3N2 Texas strain).[58]

More than a dozen studies on the effectiveness of probiotics in preventing URTIs have been conducted, with mixed results. Most studies have shown some decrease in the severity and number of illness days in participants randomly assigned to treatment groups.[59-62] Recent randomized, placebo-controlled, double-blind studies conducted over 3 winter seasons in healthy adult volunteers in Italy evaluated several synbiotic preparations. These preparations contained 3 to 5 strains of *Lactobacillus plantarum*, *L rhamnosus*, and *Bifidobacterium lactis*; lactoferrin; and prebiotics such as short-chain fructooligosaccharides (FOS) or galactooligosaccharides (GOS). The overall incidence, duration, and severity of URTI and ILI were significantly decreased in participants treated with synbiotics vs those in the placebo group.[63]

A study in Germany that evaluated the prophylactic effect of probiotics in healthy adults who took probiotics containing the strains *L gasseri* PA 16/8, *B longum* SP 07/3, and *B bifidum* MF 20/5 (5×10^7 colony forming units per tablet) daily for at least 3 months documented a significant reduction in days with cold symptoms and in the severity of symptoms and fever.[61] On the other hand, 2 studies using other strains to prevent respiratory tract infections (one study of young men undergoing French commando training and another in marathon runners) did not show any benefit of probiotics.[64,65] In addition to studying different populations, these studies may have had divergent results because probiotics have strain-specific effects on immune function.[66] Furthermore, various probiotics can have different effects on resistance to and recovery from viral infections when taken in combination with prebiotics such as FOS or GOS.[67]

In a randomized, double-blind, placebo-controlled study of children who were 3-5 years of age, participants who received either *L acidophilus* NCFM or *L acidophilus* NCFM in combination with *B animalis* subspecies *lactis* Bi-07 (vs placebo) twice daily for 6 months showed significant reductions in the incidence and duration of fever, cough, and rhinorrhea. Antibiotic use was also reduced by more than 65% and absences from daycare were reduced by approximately 30% compared with children receiving placebo.[68] Similarly, a randomized, double-blind placebo-controlled trial involving more than 500 children attending daycare in Finland showed that daily milk intake supplemented with *Lactobacillus* GG significantly reduced absences related to respiratory infections and reduced the severity of infections.[69] In a crossover study of children with cystic fibrosis who are prone to serious respiratory infections, probiotic supplementation was associated with significantly fewer episodes of pulmonary exacerbations requiring hospitalization compared with supplementation with oral rehydration solution.[70]

In a study of formula-fed infants whose diets were supplemented with *L rhamnosus* GG and *B lactis* Bb-12 or placebo from ages 2 months through 12 months, there was a significant reduction in the incidence of acute otitis media, recurrent respiratory infections, and antibiotic use among those receiving the probiotics.[71] In a similar study conducted with more than 200 infants attending Israeli child care centers, infants who received *L reuteri* had significantly fewer days with fever and fewer clinic visits, child care absences, and antibiotic prescriptions compared with those who received *B lactis* (Bb-12) or placebo, but there was no difference in the number of days with URTI.[72]

In a Swedish study, more than 900 pregnant women were randomly assigned to receive either placebo or probiotics (*L rhamnosus* GG and LC705, *B breve* Bb99 and *Propionibacterium freudenreichii* subspecies *shermanii*) for 4 weeks before expected delivery. Their infants continued to receive the same products with GOS for 6 months after birth. During 2 years of follow-up, the infants exposed to probiotics had significantly fewer URTI illnesses compared with the placebo-treated infants.[73]

Probiotics in food (eg, yogurt and kefir) or supplements are generally safe and well tolerated in adults, children, pregnant women, and even premature infants.[74,75] Sepsis-like illnesses have been described in case reports when probiotics were administered to severely immune-compromised patients.[76]

After reviewing the data, David decided it would be safe and prudent to take probiotics both for his IBS and to reduce the risk for prolonged, severe respiratory illnesses.

Homeopathic Remedies

Homeopathy (or homeopathic medicine) was developed in Germany more than 200 years ago. A central homeopathic principle is that of *similars,* or "like cures like," meaning that a disease can be cured by a substance that produces symptoms similar to those of the disease or condition. Homeopathic remedies are extremely dilute preparations of the active substance (usually a natural ingredient) that are believed to have healing properties.

Controversy exists among homeopaths about whether any homeopathic remedies are useful to prevent URTI or ILI in otherwise healthy adults. Typically, treatment depends on a broad constellation of emotional and mental characteristics as well as physical symptoms, so a remedy would not be selected purely to treat the flu or a cold per se. However, a number of homeopathic remedies are marketed as cold and flu products. Oscillococcinum is among the most popular products for ILI. A 2006 Cochrane review Oscillococcinum, including 3 prevention trials and 4 treatment trials, concluded that this remedy was not effective in preventing ILI; on the other hand, average treatment with Oscillococcinum (compared with placebo) was associated with a 0.28 day reduction in duration of ILI symptoms and marginally increased the chances that a patient would consider the treatment effective.[77] Homeopathic remedies are very safe, and although their usefulness for ILI is only marginal, these remedies can be tolerated.

Conclusion

Upper respiratory tract illnesses and influenza-like illnesses are common, as is the use of home remedies and natural products to prevent and treat them. Most natural or folk therapies have not been tested in rigorous controlled trials in diverse populations, and for those that have, studies have often had mixed results. It is prudent to ensure good hygiene, immunizations, adequate rest, and adequate fluid intake, while avoiding deficiencies of essential nutrients. Taken

prophylactically, echinacea can reduce the risk for URTI in adults by 58%; some data also support the use of garlic, American ginseng, pelargonium, and probiotics in adults to prevent or treat URTI. In children, some data suggest that vitamin C and echinacea can help reduce the risk for prolonged URTIs. The strongest data for prevention of URTI in both adult and pediatric patients are from studies on probiotics; additional research is necessary to determine optimal doses and to compare the effectiveness of various combinations of different probiotics with and without different prebiotic compounds. Little research has addressed the role of natural products in preventing or treating ILI. Although studies of black elderberry and andrographis are promising, no research has evaluated the optimal roles of these products with atypical H1N1 influenza infections. Aside from common sense precautions (avoiding honey for children less than 1 year old to reduce the risk for botulism; avoid giving bacterial products to severely immunocompromised patients), natural products are generally very safe, and their use can be tolerated.

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Authors and Disclosures

Author(s)

Kathi J. Kemper, MD, MPH

Caryl J. Guth Chair for Holistic and Integrative Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina; Director, Second Opinion Clinic, Brenner Children's Hospital, Winston-Salem, North Carolina

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