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Echinacea: Remedy or Ruse?

ABSTRACT & COMMENTARY

Source: Grimm W, Muller HH. A randomized controlled trial of the effect of fluid extract of *Echinacea purpurea* on the incidence and severity of colds and respiratory infection. *Am J Med* 1999;106:138-143.

Echinacea purpurea, derived from those beautiful purple cone flowers in your garden, has been widely used for the prevention and treatment of colds and respiratory infection. Despite its popularity (Grimm and Muller point out that Germans alone spent 45 million marks on echinacea-based products in 1993), controversy exists regarding the value of this product. Grimm and Muller randomly assigned 108 patients with a history of three or more respiratory infections during the past year to receive either daily echinacea extract or a matching placebo for eight weeks, during which time the frequency and severity of respiratory illness was assessed. The extracts were prepared from the freshly expressed juices of the whole flowering plant without its roots, and contained 22% alcohol. Patients were instructed to note any symptoms suggestive of upper respiratory illness, including burning eyes, headache, joint pain, myalgia, as well as generalized weakness and fatigue. The presence and severity of illness was clinically assessed by one of two practitioners blinded to the study medication.

Unfortunately, no significant difference in the incidence, duration, or severity of colds and respiratory infections between the two groups was found. During the eight weeks of follow-up, 65% of patients receiving echinacea and 74% of the control group had at least one cold or upper respiratory illness (RR = 0.88; P = 0.33). Nevertheless, nearly half of the participants wished to continue their study medication after completion of the study, including 43% of the placebo group.

COMMENT BY CAROL A. KEMPER, MD

Various plant parts of several different *Echinacae* species have been the basis of investigation in recent years, with lots of tantalizing in vitro and in vivo data in mice and humans demonstrating

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potentially beneficial immunomodulatory properties. Polysaccharide extracts of *E. purpurea* activate murine and human monocytes and macrophages in vitro, resulting in increased IL-1, IL-6, IL-10, and TNF-a production.[1-3] Peritoneal macrophages from immunodeficient mice treated with polysaccharide extract of echinacea exhibit increased production of TNF, as well as enhanced cytotoxicity against *Leishmania enrietti* and tumor cells.[4] Most compelling was data suggesting a protective effect of echinacea extracts administered for three days to mice subsequently challenged with lethal doses of *Listeria monocytogenes* and *Candida albicans*.[5]

In addition to its potential immunomodulatory effects, echinacea may have direct antiviral properties, although the data are limited. Thompson demonstrated that a topical blend of phytochemicals of echinacea had reasonable activity in vitro against both acyclovir-susceptible and acyclovir-resistant strains of HSV-1 and HSV-2.[8]

On the other hand, a number of studies demonstrate negative results.[6,7] For example, following the administration of echinacea for four weeks to 23 patients with malignancy undergoing chemotherapy, cultured supernatants of peripheral blood cells produced levels of cytokines similar to that of cells obtained from untreated control subjects.[7]

Clinical trials in humans have also yielded conflicting results. Two earlier clinical studies reportedly found that treatment with echinacea products decreased the duration and severity of symptoms associated with upper respiratory tract infection (URTI).[9,10] However, these papers, written in German, are not included in Medline and have not been accessible. Unfortunately, Grimm and Muller found no such benefit in their study. Daily echinacea did not appear to prevent URTI in highly susceptible patients, nor did it appear to have an effect on the signs and symptoms of illness once it occurred. Additional work performed at the Center for Complementary Medicine Research in Munich involving 302 military personnel and employees of a large industrial plant also failed to demonstrate that ethanolic extracts from either of two different species of echinacea were more effective than placebo in the prevention of URTI.[11] While 37% of patients in the placebo group developed a cold or upper respiratory illness, 32% of those receiving extracts of *E. angustifolia* and 29% receiving *E. purpurea* developed a URTI (RR = 0.8; 95% CI, 0.53-1.31). The median time to upper respiratory infection was slightly more than two months, irrespective of the group assignment.

It is not surprising that variable results may have been reported. Different echinacea species and plant parts, which may have varying levels of activity, have been variously used for study. In addition, Grimm and Muller note that the study medication in one of the earlier reports contained at least 50% alcohol, which could theoretically counteract any beneficial cellular effects (it's no wonder that half the participants wished to continue their study medication!). The unusually high frequency of apparent upper respiratory illness seen in the group of patients studied by Grimm and Muller suggests that perhaps some suffered from recurrent allergic symptoms and not viral respiratory infection, in which case, echinacea would not be expected to have an effect. Furthermore, none of these earlier studies was sufficiently powered to detect smaller differences in therapeutic outcome (e.g., 10-20%).

Nevertheless, data providing support for its immunomodulatory properties and effectiveness in

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humans, as well as the widespread popularity of this product, appear sufficiently compelling to warrant its further study. Participants in future studies should be aware, however, that little-known side effects, such as the possible inhibition of sperm enzymes and motility, may occur.[12] In vitro work by Ondrizek and colleagues on washed sperm showed that sperm motility and velocity were significantly inhibited at 24 and 48 hours by high concentrations of saw palmetto, St. John's wort, ginkgo, and echinacea.

Based on a lack of conclusive data demonstrating its clinical effectiveness, the German health board recently elected to exclude echinacea from its formulary. Although working with natural products, for which standardization is an issue, provides a challenge to investigators, clinical trials could be better designed to examine the effectiveness of these products. For example, basing the assessment on the results of nasopharyngeal swabs for culture, DFA for respiratory viruses, and swab cultures for *Streptococcus pyogenes* would provide firmer endpoints for study. In addition, studies could be designed using intranasal preparations of Corona virus as a therapeutic challenge.

With billions of dollars at stake in the health food industry, the results of these kinds of studies are going to become increasingly important. Large pharmaceutical companies are attempting to obtain marketing rights to many natural products and dietary supplements, and some believe they are laying the groundwork for control of the health food industry. Despite the fact that two large European pharmaceutical companies made headline news and were fined $500 million for price fixing the vitamin market, the pharmaceutical industry is pushing the ECC to adopt international standards for regulating natural foods and dietary supplements. Under GATT, the United States may be obligated to follow suit.

For example, a recent proposal set forth by the German delegation to the United Nations/World Health Organization commission to establish worldwide standards for food and drugs states that no minerals, herbs, or vitamins can be sold for prophylactic or therapeutic use without authorization, and none can be sold in excess of established dose limits. Canada's new Food and Drug Policy restricts the sale of any substance with therapeutic effect or medical claims (e.g., St. John's wort). It is anticipated that the attendant regulation required for registration and approval of any new product will cause Canadian prices of herbal/nutritional products to double.

To be sure, consumer protection and product safety is an important government function, but do we really want only patented, pharmaceutical versions of common herbs and dietary supplements, such as ginger and St. John's wort? We should decide whether such substances should be required to meet the same safety and efficacy standards as other drugs, and how accessible they will remain without prescription in the future. ❖

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Now Take a Deep Breath! Inhalational Tobramycin

ABSTRACT & COMMENTARY

Synopsis: *Inhaled tobramycin is effective in the management of Pseudomonas aeruginosa infection in cystic fibrosis.*

Source: Ramsey BW, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. *N Engl J Med* 1999;340:23-30.

A preparation of tobramycin (tobi) for inhalational administration received FDA approval as an orphan drug at the end of 1997 for the treatment of *Pseudomonas aeruginosa* infections in cystic fibrosis on the basis of two randomized clinical trials involving more than 500 patients. In these studies, cyclical administration to patients older than 6 years of age (mean age of the participants was 21 years) with serum creatinine less than 2 mg/dL who were not infected with *Burkholderia cepacia* was associated with a significant improvement of FEV1 over baseline. The density of *P. aeruginosa* decreased during treatment periods, but returned to baseline during periods when the drug was not administered. Of note, however, is that the diminution in density of *P. aeruginosa* in sputum during periods when tobramycin as administered was progressively attenuated during the 24 weeks of cyclical therapy. Drug recipients experienced a mean of three fewer days of hospitalization and a mean of 4.4 days fewer of parenteral antibiotic therapy treatment when compared to placebo recipients. The only toxicities noted more frequently in the antibiotic recipients than the placebo recipients were transient tinnitus and voice alteration.

COMMENT BY STAN DERESINSKI, MD, FACP

The high and variable concentrations of tobramycin in sputum, as well as the adverse effects of sputum and its components on the antibacterial activity of aminoglycosides, makes interpretation of the predictive value of in vitro susceptibility tests problematic. Thus, the definition of resistance for parenteral administration does not apply to inhaled tobramycin. There is a hint, however, that high levels of in vitro resistance (MIC > 128 mcg/mL) of *P. aeruginosa* may be predictive of failure. As expected, the administration of tobramycin over this prolonged period was associated with "MIC creep;" the proportion of *P. aeruginosa* MICs greater than 16 mcg/mL increased from 13% at baseline to 23% at the end of therapy. Tobramycin inhalation was not associated with increased risk of infection with *B. cepacia*, *Stenotrophomonas maltophilia*, or *Alcaligenes xylosidans*; however, *Candida albicans* and *Aspergillus* species were isolated with increased frequency.[1]

Antibiotics, including tobramycin, have frequently been administered by inhalation in the past, in the absence of products such as TOBI that were designed specifically for this use. Whether TOBI is more effective or safer than tobramycin compounded for parenteral administration is, to my knowledge, unknown. This is an important issue given the high cost of TOBI.

The inhalational route has a number of theoretical benefits, including the potential for achievement of extremely high antibiotic concentrations in respiratory secretions and the limitation of systemic toxicity. The tobramycin concentration in sputum approximately 10 minutes after inhalation of a 300-mg dose is, however, highly variable, ranging from 35 to 7414 mcg/g (mean, 1237 mcg/g) and exhibits a rapid decline to approximately one-seventh of these early levels after two hours. Absorption is minimal, with a mean serum concentration one hour after a single 300 mg administration to children with cystic fibrosis of approximately 1 mcg/mL. It is of interest that administration by inhalation of antibiotics in liposomes is associated with greater persistence in respiratory secretions.

Administration by this route is safer than systemic administration. The PARC LC nebulizer generates particles with a mean mass diameter of 4 μm and delivers drug primarily to the airways; avoidance of delivery of drug to the alveoli presumably limits systemic absorption. Neither nephrotoxicity nor hearing loss has been described in clinical studies with this agent, although transient tinnitus has been reported. Bronchospasm may, on occasion, follow tobramycin inhalation.

TOBI is provided in single-dose ampules, each containing 300 mg of tobramycin. It is supplied in boxes of 56, providing enough drug for a q 12h 28-day supply. It is approved for use in patients with cystic fibrosis in whom it is recommended that it be administered for 28-day cycles with intervening 28 days of treatment-free cycles for a total of 24 weeks. It is administered via a PARI LC PLUS reusable jet nebulizer powered by a DeVilbiss Pulmo-Aide compressor.[2]

Unpublished evidence suggests that TOBI may also be effective in the treatment of *P. aeruginosa* infection in adults with bronchiectasis. ❖

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tration of inhaled tobramycin on respiratory microbial flora in patients with cystic fibrosis. *J Infect Dis* 1999; 179:1190-1196.
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Another Outbreak of Hemorrhagic Fever in Africa: Marburg Virus

ABSTRACT & COMMENTARY

Synopsis: *An outbreak of hemorrhagic fever resembling Ebola virus infection was demonstrated to be due to the related Marburg virus.*

Source: WHO Weekly Epidemiologic Record 1999;74(20, 21):157-164. http://www.healthnet.org/programs/promed.html#archives; http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/marburg.htm.

Beginning in april 1999, cases of hemorrhagic fever began appearing in the Democratic Republic of the Congo (formerly Zaire). While originally thought to be the result of Ebola virus infections, this outbreak has been demonstrated to be due to the related filovirus, Marburg virus.

At least 72 suspected cases of viral hemorrhagic fever (VHF) have been identified and approximately 60 patients have been reported to have died of hemorrhagic fever in Watsa and nearby Durba. However, the actual proportion of these cases that are due to Marburg virus infection remains uncertain. The outbreak has predominantly affected young males, with the majority being involved in gold mining in Durba. Intrafamilial chains of transmission have been observed.

All five patients with virologically confirmed Marburg infections died. The first of these was the Chief Medical Officer of the Watsa zone who died on April 23, 1999, and whose infection was confirmed by the National Institute for Virology in South Africa. A woman who had reportedly lived 20-30 km from Durba died on May 7 in the isolation unit of the health center. The third confirmed case was that of a gold miner who died on May 13.

COMMENT BY STAN DERESINSKI, MD, FACP

The Marburg virus has, like Ebola, a genome of a single strand of negative sense RNA and a characteristic filamentous morphology. Marburg virus was first discovered in 1967, after an outbreak of hemorrhagic fever involving laboratory workers at the Behrinc Company in Marburg and the Paul Ehrlich Institute in Frankfurt, Germany, as well as Belgrade, Yugoslavia. The 31 affected individuals had either been working with kidneys from African Green monkeys for production of cells for in vitro cultivation or had been in contact with someone who did. The virus, first characterized in Marburg, Germany, was isolated from sick monkeys in a single shipment from Uganda. Serologic studies, however, failed to identify evidence of infection in natural living monkeys captured in Uganda.

The virus was not again encountered until 1975 when three cases, including a secondary case in a treating nurse, were identified in southern Africa. After another "eclipse" period of five years, two cases, including one in an attending physician, were identified; the index case had become ill in an area of western Kenya not far from the area in which the monkeys affected in 1967 had been captured. A single case was identified in 1987 near this same area.

The clinical syndrome caused by Marburg is identical to that caused by Ebola virus. The incubation period is usually 4-10 days (mean 7 days; range 2-21 days) and is terminated by the abrupt onset of fever, headache, arthralgia, and myalgia. Bradycardia, pharyngitis, and conjunctivitis may occur and some patients develop a maculopapular measles-like skin eruption that may subsequently desquamate. The patients may then develop diarrhea, abdominal pain, and vomiting and, with the onset of hemorrhagic manifestations after the third day of illness, hematemesis, along with cutaneous manifestations of bleeding. Fluid shifts may result in edema.

Lymphocytopenia occurs early in the illness, followed by neutrophilia and thrombocytopenia. While abnormal platelet aggregation can be detected, laboratory evidence of disseminated intravascular coagulation is absent. Hemorrhagic manifestations are likely the result of endothelial damage, together with the numerical and functional platelet deficiency. Serum transaminases are elevated, with the AST being higher than the ALT.

The natural reservoirs of both Marburg and Ebola viruses remain unknown. The virus is transmitted to humans through contact with infected animals or animal tissue; person-to-person transmission occurs as the result of close contact with infected patients and body fluids. Patients with suspected filovirus infection should be isolated and barrier nursing techniques strictly enforced. ❖

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Gonna Wash That Virus Right Out of My Cells: IL-2, HAART, and HIV Eradication

ABSTRACT & COMMENTARY

Synopsis: *Replication competent HIV was undectable in peripheral blood mononuclear and lymph node cells in a small number of patients who had received both highly active antiretroviral therapy and recombinant IL-2.*

Source: Chun TW, et al. Effect of interleukin-2 on the pool of latently infected, resting CD4+ T cells in HIV-1 infected patients receiving highly active anti-retroviral therapy. *Nat Med* 1999;5:651-655.

A major barrier to virological cure in hiv infection is the persistence of virus in cellular reservoirs. The size of the pool of resting CD4+ T cells latently infected with HIV was analyzed in 26 patients who had received highly active antiretroviral therapy (HAART) for a mean of 20-21 months and whose plasma HIV RNA was less than 50 copies/mL. Fourteen of the patients also received IL-2 intravenously or subcutaneously in doses of 3-18 million units daily for five days with intervals between treatment of at least eight weeks. These 14 patients had received a mean of 10 such cycles over 39 months. Although the study was not randomized, the two groups appeared similar at baseline.

Using a quantitative micro-co-culture method whose limit of detection was 0.032 infectious units per million cells (IUPM), the median IUPM in patients receiving HAART + IL-2 was 0.032, while it was 0.440 in those receiving HAART alone ($P = 0.01$). In assays examining as many as 20 million resting CD4+ T cells, infectious virus was detectable in all the patients receiving HAART alone, but was undetectable (IUPM < 0.032) in six (42%) of the 14 IL-2 recipients.

When cells from the six IL-2 recipients with undetectable replication competent virus in this assay were examined in an assay of up to 330 million resting CD4+ T cells, the median IUPM was 0.0069 and no infectious virus could be detected in three of the six. A repeat of this high-input assay 4-5.5 months later also failed to detect infectious virus in these three, despite the fact that a small fraction continued to contain proviral DNA (10-98 copies per million cells).

Excisional lymph node biopsy was performed on two of the patients in whom replication competent virus could not be detected in peripheral blood cells in the high-input assays. Despite culture of 40-50 million cells highly enriched for CD4+ T cells and macrophages, replication competent virus was not detected. Once again, however, a small proportion of cells contained proviral DNA.

COMMENT BY STAN DERESINSKI, MD, FACP

Several recent studies have demonstrated the persistence of latently infected CD4+ cells in patients receiving HAART for prolonged periods and in whom virus was not detectable in plasma. These findings have led to a discounting of the notion that HAART could lead to viral eradication. In fact, recent analyses have suggested that the decay half-life of these latently infected cells is such that 10-40 years of HAART would be required before viral eradication could be anticipated.

IL-2 administration to patients not receiving antiretroviral therapy commonly induces a transient burst of viral replication, probably as a consequence of the release of pro-inflammatory cytokines, such as TNF-a. The latter interacts with NFkB, which in turn is transported to the cell nucleus and upregulates HIV replication after interaction with the viral LTR. Thus, it is theorized that IL-2 may be capable of contributing to the elimination of latently infected cells as a result of their activation.

Increased viral replication may lead directly to cell death or may increase the cell's vulnerability to the immune system by increasing viral antigen display to immune cells whose competence may have been enhanced by IL-2 administration. GM-CSF may play a similar role in macrophages. The use of therapeutic vaccination in this setting has been recommended as another means to achieve this end. The recent observation of lack of viral resurgence after treatment discontinuation in a few patients whose effective HAART was repeatedly interrupted has been interpreted to suggest that viral control was the consequence of "self-immunization."

Chun and colleagues acknowledge a number of drawbacks in their study, chief of which is the lack of randomization. Nonetheless, their observation is intriguing. However, to know what it means will require a simple maneuver—stopping HAART with careful subsequent observation. It may be desirable, however, to assay for virus in other cellular reservoirs in the patients in whom replication competent virus could not be detected prior to discontinuation of therapy. ❖

Necrotizing Fasciitis After Varicella: An Association with Ibuprofen Use?

ABSTRACT & COMMENTARY

Synopsis: *A case-control study found an association between ibuprofen use and the development of necrotizing fasciitis in children with varicella.*

Source: Zer DM, et al. A case-control study of necrotizing fasciitis during primary varicella. *Pediatrics* 1999;103: 783-790.

Zer and associates at the children's hospital in Seattle were impressed with what appeared to be an increase in the number of invasive Group A streptococcal (GAS) infections, including cases of necrotizing fasciitis (NF) complicating varicella that were seen in their institution in 1993-1995. Previous reports had shown an eight times increased frequency of the use of ibuprofen in children who developed invasive GAS infections compared to controls; however, this increase was not statistically significant.[1]

Nineteen children were admitted to their hospital with NF complicating primary varicella. Demographic data, clinical parameters, and possible risk factors in these 19 children were compared to a control group of 29 children hospitalized with soft tissue infections other than NF within three weeks of varicella. There was no difference between the groups in clinical manifestations such as fever, pain, swelling, and erythema; use of acetaminophen and antibiotics was also similar. However, 9/19 cases with NF had used ibuprofen prior to hospitalization compared to 4/29 controls. The association was even stronger in only those NF cases with documented GAS infections, where 8/16 cases used ibuprofen compared with 0/8 controls (P = 0.02).

Several reasons for this apparent association have been suggested. These include a masking of local symptoms that might delay diagnosis as well as effects of ibuprofen on suppressing neutrophil function and augmentation of inflammatory cytokine production.

Although proof of an association of ibuprofen use and invasive GAS infections including NF would require a large-scale study—similar to the ones that showed a causal link with aspirin use and Reye's syndrome[2]—pediatricians should discourage the use of ibuprofen in children with varicella until more information is available. Acetaminophen is the best alternative. This serious syndrome is also further ammunition for advocating routine varicella immunization. (*Dr. Louis M. Bell is Associate Professor of Pediatrics [Infectious Diseases], University of Pennsylvania School of Medicine, Philadelphia, PA.*) ❖

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CME Questions

1. **In children with primary varicella, all of the following are correct *except*:**
   a. There may be a causal relationship between the use of ibuprofen and invasive GAS including NF.
   b. Acetaminophen is the preferred analgesic/antipyretic.
   c. Ibuprofen's anti-inflammatory actions may delay diagnosis.
   d. Children who have NF have more severe local manifestations than children with other soft tissue infections.

2. **Which of the following is correct with regard to inhalational tobramycin (TOBI)?**
   a. Peak serum concentration after a 300 mg dose is approximately 10 mcg/ML.
   b. Peak sputum concentration after a 300 mg dose is approximately 10 mcg/mL.
   c. Neither nephrotoxicity nor hearing loss was reported in clinical trials of this drug in cystic fibrosis.
   d. It should be administered to patients with *P. aeruginosa* infections and cystic fibrosis in a dose of 300 mg every other day.

3. **Which of the following is *incorrect* with regard to Marburg virus infection?**
   a. The recent outbreak (April-May 1999) of hemorrhagic fever in the Democratic Republic of the Congo has predominantly affected young males, particularly those involved in gold mining.
   b. The Marburg virus is an RNA virus.
   c. Marburg virus causes a disease that is much milder than that caused by Ebola virus, with a low case-fatality ratio.
   d. Secondary human cases due to Marburg virus infection have been observed to occur.

In Future Issues:

Viral Load Decay Following Reinitiation of HIV Therapy

UPDATES

By Carol A. Kemper, MD

Megace and Thromboembolic Disease

Source: Koller E, et al. *Nutrition* 1999; 15:294-298.

Megestrol acetate (megace) is used extensively in the treatment of wasting in patients with AIDS and malignancy. Because it is a progestational agent, there is concern that it may affect clotting pathways, resulting in increased coagulability and thromboembolic risk in some patients. Koller and colleagues from the Center for Drug Evaluation at the FDA investigated the occurrence of 92 episodes of thromboembolism in 90 patients receiving megestrol acetate who were reported to the FDA between 1970 and 1997. Events included pulmonary emboli (n = 45), deep venous thrombosis (n = 38), central retinal vein occlusion (n = 3), and, in one patient each, superficial venous thrombosis, axillary vein occlusion, superior vena caval occlusion, brachiocephalic artery thrombosis, and internal jugular and subclavianvein occlusion. Events generally occurred within the first three months of drug use.

Only 11 of the 90 had AIDS (12.2%). There was no apparent difference in the daily dose between AIDS and nonAIDS patients. However, the average dose of megestrol acetate was significantly lower in patients with pulmonary emboli (mean, 490 mg/d) compared with those with deep venous thrombosis (mean, 1554 mg/d). No other risk factor could be identified in this retrospective survey, although Koller et al acknowledged the difficulties in the collection of key information years after an event. In addition, underlying conditions that may have predisposed patients to thrombosis, such as protein C deficiency, could not be assessed.

Fewer patients with AIDS and thromboembolic events were reported than those with malignancy, possibly because many patients with AIDS are younger, male, and have less underlying disease, and are, therefore, less predisposed to thromboembolic disease. While clinicians should be aware of the remote possibility of thromboembolism in their patients with AIDS, Megace remains a safe and effective agent for use in those with wasting. ■

Household Exposure to Hepatitis A Warrants Vaccination

Source: Sagliocca L, et al. *Lancet* 1999; 353:1136-1139.

Sagliocca and colleagues from Naples, Italy, investigated the protective efficacy of hepatitis A vaccine in household contacts of patients with sporadic hepatitis A infection. Households were randomly assigned to receive either hepatitis A vaccine or no vaccine. Based on earlier clinical trial data demonstrating that 96% of adults receiving 1440 ELISA units of hepatitis A vaccine developed protective titers within four weeks of inoculation, the selected dosages used in this study were 1440 ELISA units for adults and 720 ELISA units for children. All vaccine recipients were vaccinated within eight days of onset of symptoms in the index case. Serologies were obtained at baseline, 14, and 45 days.

About one-third of the participants were immune at baseline, and an additional nine patients had evidence of positive IgM antibody and were classified as "co-infected." No household contact developed symptoms of acute hepatitis A infection within two weeks of onset of symptoms in the index case.

A statistically significant benefit to hepatitis A vaccination in household contacts resulted in premature study closure. Secondary infections occurred in only two of 71 (2.8%) households in the vaccine group compared with 10 of 75 households (13.3%) in the nonvaccine group. Among household contacts, two of 197 (1.0%) of those receiving vaccine vs. 12 of 207 (5.8%) of those in the nonvaccine group developed secondary infection. The protective efficacy of vaccine was 82%. Sagliocca et al estimated that vaccination was required in 18 individuals to prevent secondary infection in one—at a cost of about $900 in the United States. Although the study was uncontrolled, similar beneficial results were obtained in a recent effort to halt an outbreak of hepatitis A infection in Native Americans in Alaska. Clinicians should recognize this as an opportunity to quickly administer hepatitis A vaccine to household contacts of patients with known or suspected hepatitis A infection. ■

Pinworms and Urinary Tract Infections

Source: Ok UZ, et al. *APMIS* 1999; 107:474-476.

Ok and colleagues explored the possible relationship between *Enterobius vermicularis* (pinworms) and urinary tract infection (UTI) in young girls in Turkey. Using the standard cellophane method, pinworms eggs were found in 20 of 55 (36.4%) young girls with UTI. In contrast, only nine of 55 (16.4%) young girls who had never had a UTI had evidence of pinworms ($P < 0.05$). Ok et al suggest that pinworms may be a risk factor for UTI in little girls and advise close examination with nighttime application of cellulose tape to both the perianal and peroneal areas in any young girl with a UTI. ■