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INFECTIOUS DISEASE ALERT®

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Oral Therapy for Febrile, Neutropenic Patients

ABSTRACTS & COMMENTARY

Sources: Freifeld A, et al. A double-blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during cancer chemotherapy. *N Engl J Med* 1999;341:305-311; Kern WV, et al. Oral versus intravenous empirical antimicrobial therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy. *N Engl J Med* 1999;341:312-318.

Freifeld and colleagues conducted a randomized, double-blind, placebo-controlled trial comparing oral ciprofloxacin (750 mg q8h) and amoxicillin/clavulanate (500 mg q8h) with intravenous ceftazidime (2 g q8h) for the empiric treatment of febrile neutropenic cancer patients. All patients were hospitalized during the period of fever and neutropenia. Neutropenia was expected to last for no more than 10 days, and patients were free of serious other medical conditions, abdominal symptoms, signs of catheter-related infection, and new pulmonary infiltrates. Criteria for changes in the initial regimen were prospectively defined. Empirical therapy was considered successful if the patients survived the episode of fever and neutropenia without modification of the regimen or evidence of active infection at resolution.

There were a total of 116 episodes in each treatment group. Infection was documented in approximately one-third of episodes; most were soft tissue or mucosal infections. There were five bacteremias in the oral therapy group and 12 in the intravenous therapy group. Treatment efficacy was similar in both groups (71% in the oral therapy group, 67% in the intravenous therapy group). Failure in the intravenous therapy group was more likely to have been due to the need to add anti-infective agents (32%) than in the oral therapy group (13%). Failure in the oral therapy group was more likely to be due to intolerance of the regimen (16%). Fever resolved by day 5 in 90% of all episodes. There were no deaths.

In a similar, but unblinded study, Kern and colleagues randomized patients to receive either oral ciprofloxacin (750 mg q12h) plus amoxicillin/clavulanate (625 mg q8h) or ceftriaxone (2 g daily) plus

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amikacin (20 mg/kg daily). The anticipated duration of neutropenia was 10 days or less, and patients with serious complicating illness or evidence of catheter infection were excluded. Patients were hospitalized for the duration of the fever. Successful empiric therapy required resolution of therapy for three consecutive days, resolution of signs of infection if present on entry, eradication of the original pathogen, and lack of recurrence for one week after the end of therapy. The success rate of evaluable patients assigned to oral therapy was 86% (138/161); the success rate of patients receiving intravenous therapy was 84% (127/151). Twelve percent of the patients were bacteremic. There were six deaths due to infection, two in the oral therapy group and four in the intravenous therapy group. Rates of secondary infection and adverse events were similar in the two treatment groups. Patients in the oral therapy group had a high rate of gastrointestinal symptoms (26%), while only patients receiving IV therapy experienced nephrotoxicity (4%) or catheter-related complications (11%).

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COMMENT BY ROBERT MUDER, MD

The current standard of treatment for cancer patients with fever and neutropenia consists of administration of broad-spectrum intravenous antibiotic therapy.[1] However, previous studies have indicated that certain febrile, neutropenic cancer patients are at relatively low risk for serious complications.[2] These include ambulatory patients who are free of serious comorbid illness or uncontrolled malignancy. Preliminary trials have indicated that these patients might be successfully managed with oral therapy. These two recent randomized trials confirm that empiric oral therapy is as safe and effective as standard, broad spectrum intravenous therapy. Although the two studies used somewhat different study designs and drug regimens, the patient populations studied and the results were quite similar.

Several important cautions are in order, however. The patients in both trials were carefully selected for limited, anticipated duration of neutropenia, and for the absence of complicating medical conditions. Further, patients were hospitalized until resolution of fever in one trial, and resolution of fever and neutropenia in the other. Patients could be carefully monitored for signs of clinical deterioration or drug toxicity, and appropriate changes in regimen or institution of supportive care could be undertaken. Because oral therapy is less expensive than intravenous therapy, and because oral therapy can be given as an outpatient, one can easily envision pressure by insurers or HMOs to treat low-risk episodes of febrile neutropenia on a purely outpatient basis. This would be premature, and potentially unsafe. In the study of Freifeld et al, for example, 4% of patients suffered a serious adverse event such as hypotension or cecitis. All survived; however, any delay in recognition or treatment might well have been disastrous.

It may be that certain febrile neutropenic patients can, with appropriate careful monitoring, be managed with oral therapy on an outpatient basis. Identification of appropriate patients and regimens will require additional well-designed trials. Until these are completed, I agree with the authors of the accompanying editorial[3] that management of episodes of febrile neutropenia should occur in the inpatient setting. ❖

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The Will to Live

ABSTRACT & COMMENTARY

Synopsis: *A survey of 51 persons with HIV infection found that most were satisfied with their lives. In response to a hypothetical question, nearly half were unwilling to sacrifice any remaining life expectancy for better health.*

Source: Tsevat J, et al. The will to live among HIV-infected patients. *Ann Intern Med* 1999;131:194-198.

If you were ill with a chronically disabling disease, would you be willing to trade longevity for a shorter but healthier life? This intriguing question was posed to 51 HIV-infected patients with varying levels of disease progression, along with questions regarding their health status, quality of life, life satisfaction, as well as attitudes toward family, friends, and religion.

Surprisingly, 71% of the patients were delighted, pleased, or satisfied with their lives. Only 6% were dissatisfied or unhappy—and none indicated that they thought their lives were terrible. While 47% felt their life was getting better, 41% felt it was stable. The remaining 12% thought it was getting worse or did not know. Women were much more likely to be satisfied with their life, as were persons who were at "peace with God and the universe," as well as those who had stopped using injection drugs. When asked whether their life was better than before they knew they were infected with HIV, 74% of women responded "yes" vs. 39% of men (P = 0.034). There was no association between life improvement following a diagnosis of HIV and the number of years of diagnosis, stage of disease, or use of protease inhibitor therapy.

Most surprisingly, 47% of patients were unwilling to sacrifice any years of life for better health. At most, patients were willing to consider a trade-off of 5% of their remaining life expectancy for excellent health. Persons who felt better, had less fatigue, or less advanced disease were at peace with the universe, and those with children, as well as men, were less willing to sacrifice longevity. In something called a "standard-gamble score," patients were, on average, willing to risk a 20% chance of death for perfect health. There was a wide range of response to this question, however; 41% of patients were unwilling to accept more than a 1 in 200 chance of death in exchange for perfect health.

COMMENT BY CAROL A. KEMPER, MD, FACP

Tsevat and associates suggest that their data show that patients with HIV strongly prefer quantity to quality of life. On closer inspection, however, it appears that factors other than health may be more important to the sense of life satisfaction and the will to live. Directing attention to other areas of these patients' lives, such as improved living conditions, encouraging drug and alcohol treatment, and addressing psychological and spiritual issues, may have as much or greater effect on the quality of life than medical care alone. In addition, these data suggest that women may have entirely different coping mechanisms for dealing with poor health that deserve further examination in the context of HIV. There is something inspirational in these data—that many patients with HIV, despite being faced with poor health, social ostracism, and declining economic station, nevertheless have found a way to treasure life. ❖

Reduction of the Risk of Vertically Transmitted HIV by Cesarean Section

ABSTRACT & COMMENTARY

Synopsis: *Elective cesarean section reduces the risk of transmission of HIV-1 from mother to child independently of the effects of treatment with zidovudine.*

Source: The International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1: A meta-analysis of 15 prospective cohort studies. *N Engl J Med* 1999;340:977-987.

Data from 15 prospective cohort studies involving HIV-infected mothers were subjected to meta-analysis. A uniform definition of "elective" cesarean section was used (i.e., one that was performed before the onset of labor or rupture of the membranes). The data were adjusted for receipt of retroviral therapy, maternal stage of disease, and birth weight. The likelihood of vertical transmission of HIV-1 was reduced approximately 50% with elective cesarean section as compared to other modes of delivery (vaginal, nonelective cesarean section). The likelihood was reduced by approximately 87% with elective cesarean section and receipt of retroviral therapy during the prenatal, intrapartum, and neonatal periods as compared to other modes of delivery and the absence of therapy. Among mother-child pairs receiving

appropriate antiretroviral therapy, the rates of vertical transmission were 2.0% among 196 mothers who underwent elective cesarean section and 7.3% among the 1255 mothers with other modes of delivery.

COMMENT BY WARREN ANDIMAN, MD, FAAP

It has been known for at least several decades that some viral pathogens pass most frequently from mother to infant, not in utero, but at the time of delivery. These microorganisms share particular characteristics: they are found in blood in very high titer or they are shed in large numbers in the female genital tract. Hence, as the baby passes through the birth canal, virus particles enter the infant's body by way of the mucous membranes of the mouth, nose, or conjunctiva or through small tears in the skin. In addition, blood may be "transfused" from mother to baby during labor contractions. Obstetricians and pediatricians have learned that vertical transmission of herpes simplex virus can be interrupted, in most cases, if women actively shedding virus deliver by cesarean section within four hours of rupture of the membranes. Mother-to-child transmission of hepatitis B can be controlled if babies born to surface antigen-positive mothers receive hepatitis B hyperimmune globulin at birth, followed by serial vaccinations with bioengineered recombinant hepatitis B surface antigen. HIV shares a number of biologic characteristics with both herpes simplex and hepatitis B. Thus, it is not surprising that cesarean section has been entertained as one among several methods that might be used to avert mother-to-child transmission of the virus.

The report by the International Perinatal HIV Group, a consortium of five European and 10 North American prospective cohort study groups, pooled individual patient data on 8533 mother-child pairs and showed that elective cesarean section significantly reduced the risk of vertical transmission of HIV, independent of the already proven benefits of treatment of mother and infant with zidovudine. The two major advantages of this study over previous attempts to show a salutary effect of cesarean section were the large sample size and the application of uniform definitions that clarified the differences between elective and nonelective cesarean section.

The findings of this study are likely to affect obstetrical practice in the United States, at least for the time being. By combining antiretroviral therapy of mother and child with elective cesarean section, the risk of vertical transmission of HIV can be reduced approximately nine- to tenfold, to 2%, a long sought-after goal. Nevertheless, the durability of the study's results may be limited. The study failed to take into account a number of critical covariates, either because they were not collected uniformly by all participants or because the study ended before current pharmacologic interventions could be adequately evaluated. For example, data on viral load were not included in the analysis, and it is not inconceivable that viral load may greatly influence the risk of vertical transmission. Furthermore, most mother-child pairs included in the analysis by the International Perinatal HIV group received monotherapy or dual antiretroviral therapy. It will be critical to learn if receipt of highly active poly-antiretroviral therapy by childbearing women, a practice that has become commonplace only in the past two years, reduces vertical transmission more dramatically than previous regimens. Such a finding may eliminate or significantly abrogate the need for cesarean section.

In the meantime, women's health care providers must use the data now available to weigh the risks of surgical morbidity against the benefits of cesarean section. Unfortunately, the benefits of cesarean section may not apply to countries in the undeveloped world, the site of the great majority of incident cases of perinatal HIV infection. In such settings, gestational age cannot be assessed accurately; hence, an increased frequency of preterm births could be expected following elective cesarean section. Also, the hazards associated with surgical procedures of any kind may outweigh the benefits. Alternative solutions, both medical and surgical, to the high prevalence of pediatric AIDS in less-developed countries remain elusive. (*Dr. Andiman is Professor of Pediatrics and Director of the Pediatric HIV/AIDS Program at the Yale-New Haven Children's Hospital and the Yale University School of Medicine.*) ❖

Antibiotic Resistance in Pediatric *E. coli* Urinary Tract Infections

ABSTRACT & COMMENTARY

Synopsis: *Risk factors for antimicrobial resistance among E. coli UTIs were identified in a population of children seen at a tertiary care center in Ontario over a two-year period. Increasing resistance of E. coli to common, inexpensive, and well-tolerated antibiotics was noted and their use as prophylactic agents should be re-examined.*

Source: Allen UD, et al. Risk factors for resistance to "first-line" antimicrobials among urinary tract isolates of *Escherichia coli* in children. *CMAJ* 1999;160:1436-1440.

Allen and colleagues studied 1636 consecutive *Escherichia coli* isolates from 967 children with urinary tract isolates (UTI) at a children's hospital

in Canada over a two-year period (1992-1994). Their goal was to determine the prevalence of resistance to commonly used antibiotics for treatment of UTI and to identify risk factors associated with this resistance. Risk factors were identified using a case-control study in which 274 children with *E. coli* resistant to trimethoprim-sulfamethoxazole (Tmp-Smx) were matched with children with Tmp-Smx-sensitive isolates.

There was a disturbingly high prevalence of resistance among *E. coli* isolates to ampicillin (45%) and Tmp-Smx (31%) and to both ampicillin and Tmp-Smx (22%). As expected, resistance to nitrofurantoin (2%), gentamicin (3%), and cefotaxime (0.1%) was much less. Approximately 1.7% of the isolates were resistant to both ampicillin and gentamicin, which, as Allen et al point out, may begin to have implications in the choice of empiric antibiotic therapy for neonatal sepsis in their population.

Risk factors for antibiotic resistance included: 1) antibiotic treatment for more than four weeks in the preceding six months (OR*14); 2) the presence of urinary tract abnormalities including vesicoureteral reflux (OR 4); 3) hospitalization within the past year (OR 2-4); 4) the presence of a malignant disease (OR 5); 5) antibiotic prophylaxis for immunodeficiency (OR 15); and 6) older age, since children younger than 2 years were three times less likely to be infected with resistant organisms. The incidence of pyelonephritis was not greater in the Tmp-Smx-resistant group.

Allen et al conclude that the role of commonly used, inexpensive antibiotics such as ampicillin and Tmp-Smx in the outpatient treatment and prevention of urinary tract infections requires re-examination, particularly in children who have recently received antibiotic therapy.

COMMENT BY THOMAS L. KENNEDY, MD, FAAP

We are all concerned about the growing problem of antimicrobial resistance spurred on by the extensive use, and sometimes overuse, of antibiotics. Knowing the magnitude of the problem for a given locale can be helpful in the choice of antibiotics. Additionally, however, identifying other risk factors can assist not only in the selection of antibiotics, but also in the development of strategies to avoid antibiotic use in certain populations if possible. For years, we have worried that the administration of "first-line" drugs such as amoxicillin for prophylaxis might lead to resistance as a result of antimicrobial pressure. The finding that four or more weeks of antibiotic use in the preceding six-month period is associated with resistance appears to support that concern. The other risk factors listed above are not surprising and make sense: things such as being in the hospital, having an immuno-deficiency, or being younger and not having been treated with many courses of antibiotics. The absence of an association with pyelonephritis is somewhat surprising because, at least simplistically, one often equates more aggressive with more resistant organisms.

The findings in this study suggest that the use of nitrofurantoin, which has a low rate of resistance by *E. coli*, continues to be a good choice for urinary tract prophylaxis. It is, after all, safe, effective, and inexpensive. Unfortunately, it is not a favorite, either for parents or children, in terms of taste and acceptability, but you can't have everything. Other approaches, such as alternating antibiotics, may also demonstrate effectiveness and should be studied further. (*Dr. Kennedy is Associate Clinical Professor of Pediatrics, Yale University School of Medicine.*) ❖

**(OR = odds ratio, or the odds of having the risk factor if the condition [e.g., Tmp-Smx resistance] is present divided by the odds of having the risk factor if the condition is not present.*)

Special Feature

Updated Varicella Vaccine Recommendations

By Hal B. Jenson, MD, FAAP

The advisory committee on immunization practices (ACIP) of the Centers for Disease Control and Prevention (CDC) has issued updated varicella vaccine recommendations[1] of the original CDC recommendations published in 1996.[2] These expanded recommendations include: 1) establishing requirements for child daycare and school entry; 2) vaccination following exposure of susceptible persons to varicella, and for outbreak control; 3) expanded recommendations for vaccination of susceptible adolescents and adults at high risk for exposure or transmission; and 4) vaccination for persons with humoral immune deficiencies, and for some children infected with human immunodeficiency virus (HIV). The ACIP also reviewed postlicensure adverse events reportedly associated with the varicella vaccine.

Updated Varicella Vaccine Recommendations

Daycare and School Entry Requirements. Because the incidence of varicella is highest among children 1-6 years of age, vaccination during early childhood will have the greatest effect on reducing the incidence of disease. The ACIP now recommends that all states require that children entering child daycare facilities and elementary schools either have received

varicella vaccine or have other evidence of immunity to varicella. Because school vaccine requirements are set at the state level, there will likely be some disparity across the United States in actual requirements. Already, 10 states have enacted requirements for varicella vaccination, and additional requirements are pending in many other states. Evidence of immunity includes either: 1) varicella vaccination; 2) a physician's diagnosis of varicella; 3) a "reliable history of the disease"; or 4) serologic evidence of immunity. The ACIP also suggests that "states should also consider implementing a policy that requires evidence of vaccination or other evidence of immunity for children entering middle school (or junior high school)."

Postexposure Vaccination. There are data from the United States and Japan following varicella exposure in household, hospital, and community settings that varicella vaccine is effective in preventing illness or modifying varicella severity if given within three days, and possibly up to five days, of exposure.[3-5] The ACIP now recommends that varicella vaccine be given to susceptible persons following exposure to varicella. If exposure does not result in disease, then vaccination will provide protection for subsequent exposure. There is no evidence that vaccination during the presymptomatic or prodromal stage of varicella increases the risk for complications or vaccine-associated adverse events, or that administration of live virus vaccines to persons with pre-existing immunity is associated with any adverse effects. The need for postexposure prophylaxis of healthcare workers should be minimal because all healthcare workers should be immune to varicella (as well as to measles and rubella).[6]

Vaccination of Persons 13 Years of Age or Older. Varicella vaccine has been recommended since 1996 for susceptible persons 13 years of age or older at high risk for exposure or transmission; the updated recommendations now include susceptible adolescents and adults living in households with children as a new high-risk group. The recommendations for varicella vaccination of susceptible persons 13 years of age or older now includes: 1) persons who live or work in environments where transmission of VZV is likely, such as teachers of young children, child daycare employees, and residents and staff members in institutional settings; 2) persons who live and work in environments where transmission can occur, such as college students, inmates and staff members of correctional institutions, and military personnel; 3) nonpregnant women of childbearing age; 4) adolescents and adults living in households with children; and 5) international travelers.

Persons with Altered Immunity. The previous ACIP recommendations stated that varicella vaccine not be administered to any person with primary or acquired immune deficiency. The ACIP maintains the recommendation against varicella immunization of persons with cellular immunodeficiencies, but now recommends that persons with impaired humoral immunity may be vaccinated. In addition, some HIV-infected children, who are at greater risk for complications of varicella and zoster compared to healthy children, may now be considered for varicella vaccination. Unpublished data from the Pediatric AIDS Clinical Trial Group indicate that two doses of varicella vaccine administered to HIV-infected children with asymptomatic or mildly asymptomatic disease are immunogenic and effective. HIV-infected children who are CDC class N1 ("no signs or symptoms") or A1 ("mild signs or symptoms") and have age-specific $CD4^+$ T lymphocyte percentages ≥ 25% are eligible, and "varicella vaccine should be considered." The vaccination regimen for these children is two doses of varicella vaccine three months apart.

The vaccine has not been licensed for persons with blood dyscrasias, leukemia, lymphoma of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems. Varicella vaccine is available from the manufacturer (Merck) through a compassionate use protocol for children with acute lymphocytic leukemia (ALL) who are in remission, provided local approval by the appropriate institutional review board and informed consent have been obtained.

Update of Adverse Events Since Licensure

From March 1995 to July 1998, a total of 9.7 million doses of varicella vaccine were distributed in the United States. The Vaccine Adverse Event Reporting System (VAERS) has received 6850 reports of adverse events, approximately two-thirds of which are in children younger than 4 years of age. The most frequently reported adverse event is rash, which occurs at a rate of 37 per 100,000 vaccine doses. However, PCR analysis showed that most postvaccination rash illnesses occurring within two weeks of vaccination were caused by wild-type varicella-zoster virus. For other serious adverse events that have been reported, the rates following vaccination are lower than the expected levels after natural varicella infection or than the background rates of disease in the community. This finding confirms that vaccination is safer than natural infection, even though chickenpox in children is thought of as a benign disease.

Development of Zoster. The VAERS rate of zoster after varicella vaccination was 2.6 per 100,000 vaccine doses, less than the overall rate of zoster of 215 per 100,000 person years, or the rate among healthy chil-

dren after natural varicella infection of 68 per 100,000 person years. Cases of postvaccination herpes zoster have been confirmed by PCR to be due to both vaccine virus and wild-type virus, suggesting that some cases of zoster in vaccinees actually result from antecedent natural varicella infection.

Transmission of Vaccine Virus. Transmission of vaccine virus is rare, and has only been documented on three occasions. All three cases resulted in mild disease without complications. In one case, a 12-month-old child transmitted the virus to his pregnant mother, who elected to terminate pregnancy. No vaccine virus was found in fetal tissue by PCR analysis. The other cases involved two 1-year-old children who transmitted vaccine virus to a healthy sibling and to a healthy father. Secondary transmission has not been documented in the absence of a postvaccination vesicular rash.

Conclusions

The varicella vaccine has been used extensively with good efficacy and safety. The updated recommendations reflect the experience and results of ongoing investigations of postexposure prophylaxis and use in HIV-infected children. Immunization for varicella is an important component of the recommended childhood vaccine regimen and should be provided to all children beginning at 12 months of age, to susceptible older children to the 13th birthday, and to susceptible family members of households with children. In addition, varicella vaccine should be used for postexposure prophylaxis of susceptible persons.

It is important to ensure that all children for whom vaccination is recommended receive the vaccine. Increased varicella vaccination levels in the community will mean less circulating wild-type virus and less exposure during childhood, with a greater likelihood of disease during adulthood and the associated higher risk of serious complications, including death. (*Dr. Jenson is Chief, Pediatric Infectious Diseases, University of Texas Health Science Center, San Antonio, TX.*) ❖

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Readers are Invited...

Readers are invited to visit *Infectious Disease Alert* at the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) September 26-29 in San Francisco. Come by booth 303 in the exhibit hall of the Moscone Center during the conference. We look forward to seeing you. ❖

CME Questions

15. True statements from the latest ACIP recommendations for varicella immunization include all of the following *except*:

a. All susceptible children entering daycare or elementary school should be immunized.
b. Evidence for lack of susceptibility includes a reliable history or diagnosis of varicella, a previous immunization, or a positive serologic test.
c. All susceptible children with HIV infections should be immunized.
d. Immunization has a higher rate of complications than natural infection.

16. Risk factors for Tmp/Smx antibiotic resistance of cultured *E. coli* include all of the following *except*:

a. age older than 6 years.
b. antibiotic treatment for more than four weeks in the preceding six months.
c. a history of pyelonephritis.
d. grade 4 vesico-ureteral reflux.

In Future Issues:

Treatment of Lyme Encephalopathy with Intravenous Ceftriaxone

UPDATES

By Carol A. Kemper, MD, FACP

Who Put *Salmonella* in my Sand?

Source: Bolton FJ, et al. *Epidemiol Infect* 1999;122:7-13.

Gastrointestinal symptoms are more frequent in swimmers who bathe or swim in fecally contaminated coastal waters, but simply sunbathing on the beach has not been considered a big risk factor for enteric disease. Could sand act as a sieve for nasty bacterial organisms that end up in coastal waters?

To examine this question, a total of 182 samples of sand were collected over a four-week period from four different beaches in England and examined for the presence of thermophilic *Campylobacter* and *Salmonella*. Two of the beaches were in compliance with British water directives, but two were located within 1-3 miles of sewage pipes and/or fecally contaminated agricultural run off. Separate samples of dry sand found just below the high water mark as well as wet sand from the water's edge at low tide were collected from each beach.

Overall, 45% of the samples contained *Campylobacter* spp. and 6% contained *Salmonella*. *Salmonella* were isolated from 9% of specimens obtained from noncompliant beaches vs. 2% of the compliant beaches, but *S. enteritidis* and *S. typhimurius* were isolated from both. The major human pathogens, *C. jejuni* and *C. coli*, were more frequently isolated from the noncompliant beaches, but other *Campylobacter* spp. commonly associated with seagulls and migratory birds were more prevalent in sand from the compliant beaches. Wet sand was more frequently contaminated with *Campylobacter* (24-77%), but about one-third of the dry sand samples were also contaminated (10-54% of specimens). These data suggest that even dry sand may function as an effective reservoir for *Campylobacter* despite its minimal water content.

While the risk to public health is difficult to assess from this information, it is reasonable to stick to beaches distant from fecally contaminated run off, to avoid foods and beverages contaminated with sand, and to shower once you get home from the beach. On a similar note, a municipality in the San Francisco East Bay recently banned children in diapers from visiting public waterways, including lakes, streams, and beaches. This seems like an overly extreme response to a complex issue, especially given the numerous other potential sources for public waterway contamination. ■

Does Size Matter?

Source: Ferrer M, et al. *Ann Intern Med* 1999;130:991-994.

The presence of a nasogastric tube in intubated and mechanically ventilated patients is a significant risk factor in gastroesophageal reflux and microaspiration, but how much does the size of the tube matter? It turns out, maybe not much at all. Despite the commonly held belief that smaller tubes reduce the risk of microaspiration, this study suggests otherwise.

Two different sizes of nasogastric tubes (2.85 mm and 6.0 mm) were placed, in randomized order, in 17 intubated, but clinically stable, patients in an intensive care unit. Pharyngeal aspirates were measured for up to 17 hours after tube placement using radioactive technetium colloid instilled in each patient's stomach. After 72 hours, the alternate tube was placed and the measurements were repeated. Although the amount of pharyngeal reflux significantly increased over the time the tube remained in place, no difference was observed at any time point between the two tubes, with the possible exception of sinusitis, which was not examined in this study. There does not appear to be much basis for the continued use of these smaller tubes, which are more expensive and generally more difficult to insert than the standard nasogastric tubes. ■

Terbinafine Superior to Itra in Toenails

Source: Evans EG, et al. *BMJ* 1999;318: 1031-1035.

Because therapeutic concentrations of itraconazole persist in the nail bed for several days, some experts advocate that, for the treatment of onychomycosis, the administration of this azole should be cycled. In contrast to itraconazole, which is fungistatic, terbinafine is a newer allylamine antifungal agent that has cidal activity against most dermatophytes. In a double-blind, randomized, controlled trial, 496 patients with onychomycosis were randomized to receive either continuous terbinafine 250 mg daily for either 12 or 16 weeks or itraconazole 400 mg daily for one week of every month for 12 or 16 weeks. Eligible patients had distal subungual or total dystrophic nail disease confirmed by culture as well as KOH.

Continuous terbinafine was substantially better, resulting in clinical cures (defined as 100% toenail clearing) in 54% of patients at 12 weeks and 60% of patients at 16 weeks. In contrast, only 32% of patients receiving itraconazole were clinically cured. Mycological cures were achieved in 76-80% of patients receiving terbinafine and 38-49% receiving itraconazole. Both drugs were well tolerated and the frequency of side effects was similar. While daily terbinafine is superior to intermittent itraconazole in the treatment of onychomycosis, clinicians should keep in mind that 20-40% of patients may fail three to four months of therapy and require a longer course of treatment. ■