Drug Resistance Looms in Traveler's Diarrhea

BY MIRIAM E. TUCKER

BETHESDA, MD. — The level of fluoroquinolone resistance in enteric pathogens has increased considerably over the last decade among travelers to Mexico, Guatemala, and India, based on an analysis of stool samples from more than 400 adult travelers to those countries.

But susceptibility has remained fairly stable for the poorly absorbed agent rifaximin as well as for azithromycin, suggesting that those agents may represent more suitable options for self-initiated treatment and prophylaxis of traveler's diarrhea, Dr. Jeanette Ouyang-Latimer said at the annual conference on antimicrobial resistance sponsored by the National Foundation for Infectious Diseases.

"It's important to monitor susceptibility patterns of enteropathogens causing traveler's diarrhea over time, especially when we've seen more liberal use of antibiotics for. The further increase in fluoroquinolone resistance may make it less ideal for those uses," said Dr. Ouyang-Latimer of Baylor College of Medicine, Houston.

VITALS

Major Finding: In Mexico, Guatemala, and India, the proportion of enterotoxigenic *E. coli*–resistant strains was 24% to levofloxacin, 20% to ciprofloxacin, 18% to azithromycin, 17% to rifaximin, and 5% to ceftriaxone.

Data Source: A study of stool samples from 434 travelers to India and Latin America.

Disclosures: Dr. Jeanette Ouyang-Latimer stated that she has no relevant conflicts of interest. The principal investigator, Dr. Herbert L. DuPont, has received speaking honoraria and/or research grants from several companies, including Salix Pharmaceuticals, Merck Vaccine Division, IOMAI, Intercell, Optimer Pharmaceuticals, and Santarus.

The stool samples were taken during 2006-2008 and were tested for enterotoxigenic *Escherichia coli* (ETEC), *Salmonella*, *Vibrio*, *Shigella*, *Aeromonas*, and *Plesiomonas*. The minimum inhibitory concentration (MIC) was determined by agar dilution for the antibiotics ampicillin; tetracyclines, including doxycycline, nalidixic acid, ceftriaxone, and trimethoprim-sulfamethoxazole (T/S); fluoroquinolones, including ciprofloxacin and levofloxacin; and azithromycin and rifaximin.

The most common agent was ETEC, with 270 samples isolated from 291 travelers to Mexico/Guatemala (grouped together as "Latin America") and 98 of 143 travelers to India. Campylobacter was more common in samples from India than from Latin America (17 vs. 6).

From all the regions combined, the proportion of ETEC-resistant strains was 24% to levofloxacin, 20% to ciprofloxacin, 18% to azithromycin, 17% to rifaximin, and 5% to ceftriaxone. Resistance was much higher—around 50% each—to the older, less-used agents ampicillin, nalidixic acid, and T/S.

Contrary to previous reports from Southeast Asia, the campylobacter isolates did not show significant fluoroquinolone resistance, but 22% did show resistance to rifaximin, Dr. Ouyang-Latimer said.

'The further increase in fluoroquinolone resistance may make it less ideal' for self-initiated therapy and prophylaxis of traveler's diarrhea.

By location, ETEC resistance to levofloxacin was far greater in India than in Latin America (41% vs. 20%). Azithromycin resistance also was higher in India than in Latin America (24.5% vs. 16%). All of the resistant campylobacter strains were seen in India, with 29% of the total showing rifaximin resistance.

The MIC at which 90% of the strains tested were inhibited (MIC90) from these samples was compared with MIC90 values previously reported from travelers to the same regions in 1997 (Antimicrob. Agents Chemother. 2001;45:212-6).

For ETEC, MIC90 levels had increased by twofold or greater for all the commonly used antibiotics. For ciprofloxacin, ETEC strains demonstrated a ninefold increase in resistance, from 3% in 1997 to 20% in 2006-2008. Levofloxacin resistance also increased dramatically among ETEC, from 3% to 24%.

These findings reflect the fact that fluoroquinolones and azithromycin often can be obtained without prescriptions in these regions, she noted. In contrast, ETEC retained 80% susceptibility to rifaximin and azithromycin. Ceftriaxone also showed low levels of resistance, but this agent is not practical to use for traveler's diarrhea, since it can only be given intramuscularly or intravenously. The MIC90 levels had also dropped for T/S, but it is not often used anymore.

For campylobacter, the MIC90 seems to have decreased, but the sample size for these isolates was small, she noted.

Although rifaximin and azithromycin do appear to remain good options for traveler's diarrhea, it's still not clear whether they can be used for such enteroinvasive pathogens as salmonella or shigella, she said. ■

IBD and Rheumatic Disease Can Be Managed Concurrently

BY SALLY KOCH KUBETIN

SANTA MONICA, CALIF. — How to treat a patient with concurrent inflammatory bowel disease and rheumatic disease depends on which condition is "hot" and which is quiescent.

Using standard anti-inflammatory agents to treat the rheumatic disease is problematic because it may exacerbate the IBD. Conventional NSAIDs are associated with reversible colitis and ulceration in patients without IBD, and NSAID enteropathy—often subclinical—is present in up to 60% of patients who take these agents, according to Dr. Bennett E. Roth, director of the digestive disease center and chief of clinical gastroenterology at the University of California, Los Angeles.

Data do support the use of available cyclo-oxygenase-2 (COX-2) inhibitors in patients with both active IBD and active joint disease, Dr. Roth said at a meeting sponsored by RHEUMATOLOGY NEWS and Skin Disease Education Foundation.

Why some patients develop both IBD and arthritis is not fully understood, Dr. Roth noted. Possible explanations include the potential relocation of the immune reaction from the intestine to the joints; the activation of immune cells in the gut, draining lymphocytes that localize in the joints; and the overlap of expression of adhesion molecules that have been observed on the surface of intestinal epithelial cells and in synovial fluid. Other possibilities include the potential reactivation of T cells at the articular levels and possible T-helper 17 (Th17) cell–mediated response aided by tumor necrosis factor (TNF).

Because the joint inflammation corresponds to the activity of the disease in the gut, there is likely to be a concomitant joint response once the bowel disease is placed into remission.

IBD arthropathy can take two forms: spondyloarthropathy (SpA) and peripheral arthropathy. Each has its own course and relationship to IBD, Dr. Roth said.

The degree of SpA activity in IBD patients is independent of the IBD activity.

Among patients with both conditions, 20%-25% have sacroiliitis on x-ray; 50% of cases of sacroiliitis in IBD are asymptomatic.

Ankylosing spondylitis (AS)—be it HLA-B27 negative or positive—has a prevalence of 3%-10% in this population, according to Dr. Roth.

Rheumatologists may be the first to see signs of IBD in some of these patients. Young patients who present with axial arthropathy may be candidates for a gastrointestinal evaluation, said Dr. Roth, who is also director of the center for esophageal disorders at UCLA.

The treatment regimen for AS includes physiotherapy, 5-aminosalicylic acid (5-ASA) or immunomodulatory therapy with agents such as 6-mercaptopurine or azathioprine (6MP/AZA), or methotrexate. Fallback treatments are short courses of steroids. If these are insufficient, biologic anti-TNF antibodies may be effective.

One large study showed that infliximab was efficacious in 61% of a group of IBD patients with peripheral arthritis (Am. J. Gastroenterol. 2002;97:2688-90). Infliximab has been shown to be effective in 53% of patients with AS, regardless of the presence of concurrent IBD (Lancet 2002; 359:1187-93). Findings from randomized controlled trials of patients who had both AS and IBD and were treated with infliximab show a significant drop in BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) scores but not CDAI (Crohn's Disease Activity Index) scores (Ann. Rheum. Dis. 2004; 63:1664-9).

Peripheral arthropathy is divided into types 1 and 2 for classification purposes. Type 1 peripheral arthropathy can involve the large joints, specifically ankles, knees, hips, elbows, and shoulders, in a pauciarticular pattern.

When it comes to the treatment of type 1, Dr. Roth said that as the IBD goes, "so goes the arthritis." In other words, because the joint inflammation corresponds to the activity of the disease in the gut, there is likely to be a concomitant joint response once the bowel disease is placed into remission. Standard approaches to treating the IBD are employed, including anti-inflammatory agents such as 5-ASA and steroids with the additional use of immunosuppressants 6MP/AZA, or anti-TNF agents as needed.

Other options include a local steroid injection when possible and the use of simple analgesics. However, NSAIDs (with the possible exception of celecoxib) should be avoided.

Type 2 peripheral arthropathy involves the small joints of the hands, is persistent and polyarticular, and follows a course that is independent of the IBD course.

Treatment consists of physical therapy, simple analgesics, short courses of steroids with progression to immunosuppressive agents, and/or biologics as needed. ■

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