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A Closer Look at AEMCOLO With MMX Technology for the Treatment of Travelers' Diarrhea

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G&H Could you please provide some background on travelers' diarrhea?

BC The clinical definition refers to diarrhea that occurs during or shortly after travel, typically from a more-industrialized country to a less-industrialized country. The diarrhea is usually associated with other enteric symptoms, such as vomiting, abdominal cramping, bloating, pain, and gas.

For studies, the definition of travelers' diarrhea is more strict: 3 or more unformed stools in a 24-hour period associated with at least 1 other enteric symptom. This definition is used so that comparisons can be made across different studies. The definition is not for the diagnosis of individual travelers; it is not necessary for someone to wait until the third unformed stool to know that he or she has travelers' diarrhea.

The areas at risk for causing travelers' diarrhea include all places in the world outside of the United States, Canada, Western Europe, Australia, New Zealand, and Japan.[1] Travelers' diarrhea can occur in places where there is a breakdown in some basic hygiene sanitation that results in an increase in microbes that cause diarrheal illness. For the most part, the standard travelers' diarrhea is a bacterial illness; approximately 85% of cases are caused by bacteria.[2] The other causes are parasites, such as giardia, and viruses.[3] Sometimes norovirus can cause outbreaks, on cruise ships, for example.[4]

There is a seasonal risk in certain parts of the world. In South Asia, India, and Nepal, the risk of travelers' diarrhea is very high in the pre-monsoon months, which are April, May, June, and July. Risk decreases in autumn.

In places with a moderate to high risk of travelers' diarrhea, between 25% and 40% of travelers will develop the condition. For example, a traveler staying in Mexico for 1 or 2 weeks has an approximate 1-in-3 chance of developing travelers' diarrhea. To decrease risk, we advise travelers to be careful about what they eat and drink in these locations. For example, we tell travelers to avoid tap water and to drink bottled beverages instead. Bottled carbonated beverages are safest because they were definitely bottled at a plant. Foods that were washed in water should not be eaten. Travelers should avoid salads and buffets. The safest foods are cooked and served piping hot. It is difficult to completely adhere to these recommendations. In addition, many factors are outside of the traveler's control. For example, there may be someone working in a kitchen who is incubating an enteric infection, or a restaurant may serve food on plates or with utensils that were improperly cleaned. Therefore, risk can be minimized but never completely eliminated.

As an historical perspective, prior to 1970, physicians were not convinced that travelers' diarrhea was an infectious disease. Alleged causes included too much sun, change in diet, spicy foods, and jet lag. In 1970, with the description of the first bacterial pathogen—enterotoxigenic *Escherichia coli* (ETEC)—travelers' diarrhea was recognized as an infectious disease.[5]

G&H What are the potential long-term adverse sequelae of inflammation in travelers' diarrhea?

BC In most cases, travelers' diarrhea is an acute, self-limited illness. The symptoms resolve in approximately 3 to 5 days, and even more quickly with treatment. The vast majority of people with a bout of travelers' diarrhea get well. A small percentage, though, will develop postinfectious sequelae. The most common is probably postinfectious irritable bowel syndrome (IBS),[6,7] which can occur in 1% to 10% of people with travelers'

diarrhea. Postinfectious IBS is a continued inflammatory process that occurs when the intestine fails to downregulate inflammation. The syndrome is associated with ongoing symptoms of gastrointestinal distress. These symptoms do not always include diarrhea, but may consist of abdominal pain, changes in bowel habits, bloating, and gas. Another complication of travelers' diarrhea is reactive arthritis,[8] which is a migratory arthritis that sometimes occurs after an enteric infection. Guillain-Barré syndrome can follow *Campylobacter* infections,[9] which are a common cause of travelers' diarrhea in parts of Asia.

G&H Why is there a need for new treatments in travelers' diarrhea?

BC When travelers' diarrhea was recognized as an infectious, mainly bacterial disease, it became apparent that antibiotics were very effective in shortening the course and achieving a cure. In the 1970s, the standard treatment was to use prophylactic once-daily antibiotics to prevent travelers' diarrhea. This strategy had a remarkable impact, reducing rates of diarrhea from 40% to approximately 4%. Millions of people took antibiotics to prevent travelers' diarrhea. In 1985, this widespread use led the National Institutes of Health to convene a consensus conference on whether this was a good practice.[10] They concluded it was not, based on the rising resistance and associated adverse events.

It was soon discovered that the newly developed fluoroquinolones could effectively treat travelers' diarrhea. A patient who took a fluoroquinolone at the onset of diarrhea would feel better in 4 to 6 hours. The new strategy incorporated self-treatment, meaning doctors would prescribe an antibiotic for a traveler to take on the trip and use as needed.

There are 2 reasons why new treatments are needed: resistance and adverse events. A particular antibiotic can be used to treat travelers' diarrhea for approximately 10 years before resistance develops. The antibiotics used in the 1970s, such as doxycycline and trimethoprim-sulfamethoxazole, became ineffective because of resistance among the organisms. Fluoroquinolones, such as ciprofloxacin, are now relatively ineffective in certain parts of the world.[11] For example, infection with *Campylobacter* is not treatable with a fluoroquinolone; it is best treated with the macrolide azithromycin.[12]

Standard antibiotics, whether fluoroquinolones or macrolides, are associated with the potential for side effects.[13] The fluoroquinolones can cause tendinopathies and increase the risk of *Clostridium difficile*.

Based on these drawbacks, physicians are wary about recommending antibiotics to all travelers who have a loose bowel movement. There is a need for non-antibiotic treatments, as well as antibiotics that are safer. It is also necessary to consider the severity of the episode. In 2016, the International Society of Travel Medicine and the US Centers for Disease Control and Prevention (CDC) held a consensus conference on the management of travelers' diarrhea. One of the recommendations was that the management of travelers' diarrhea should reflect whether the episode is mild, moderate, or severe.[14] Antibiotics should not be used in patients with mild travelers' diarrhea. In some cases, they are an option for patients with a moderate episode. Patients with severe travelers' diarrhea should receive treatment with antibiotics.

> An important concern with the use of antibiotics in high-risk environments is the acquisition of ESBL-producing *E coli*.

G&H What is the impact of multidrug-resistant bacteria?

BC There are 2 important aspects to resistance. The first concerns resistance to the currently available antibiotics used to treat travelers' diarrhea.[11] The second issue is the acquisition of multidrug-resistant bacteria. The ability to study the microbiome has shown that people who visit areas at risk for travelers' diarrhea and take antibiotics become colonized with multidrug-resistant bacteria. In a Finnish study led by Dr Anu Kantele, 80% of travelers to India who took an antibiotic developed extended-spectrum beta-lactamases (ESBL), a resistant type of enterobacterium.[15] The acquisition of multidrug-resistant bacteria does not typically impact the individual, with some exceptions. Multidrug-resistant bacteria can be difficult to treat in women prone to urinary tract infections. In men with prostatitis or who have undergone a prostate biopsy, multidrug-resistant bacteria can cause infections that are difficult to treat because these bacteria are usually colonic and seed the urinary tract and the prostate. After returning home, the travelers can also transmit multidrug-resistant bacteria to other people.

G&H How is the management of travelers' diarrhea evolving?

BC The first major change in the management of

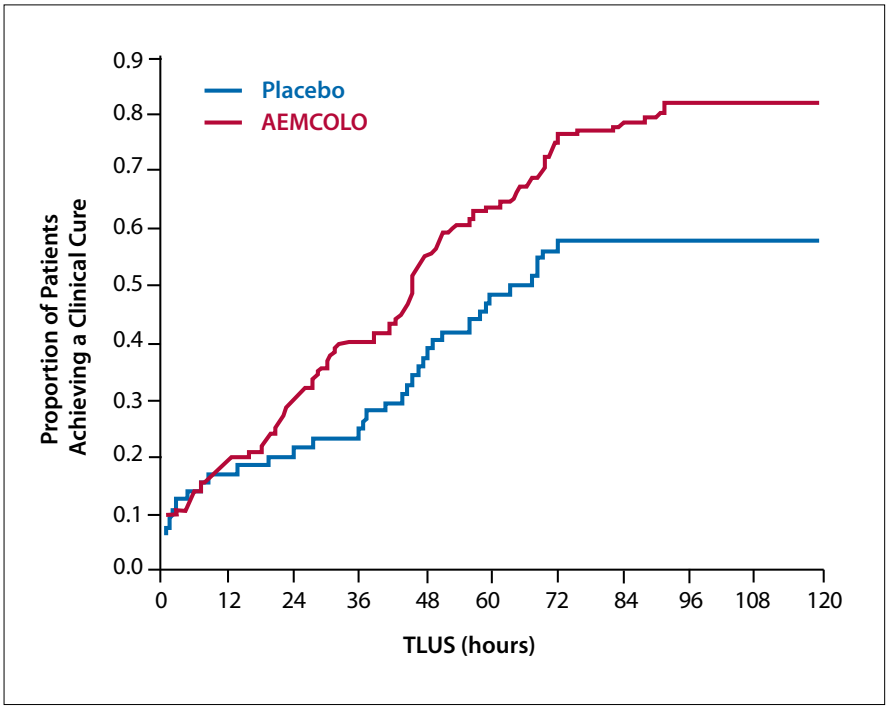

Figure 1. Clinical cure rates in a phase 3 trial comparing AEMCOLO vs placebo. TLUS, time to last unformed stool. Adapted from DuPont HL et al. *J Travel Med*. 2014;21(6):369-376.[22]

travelers' diarrhea was the availability of a nonabsorbable antibiotic. The first nonabsorbable antibiotic, rifaximin, was initially approved by the US Food and Drug Administration (FDA) in 2004 for the treatment of travelers' diarrhea at a dose of 200 mg 3 times daily.[16] Rifaximin is an ansamycin. Studies showed that rifaximin was not absorbed into the bloodstream, so it is considered to be safer than systemic antibiotics.[17] It did not cause the adverse effects associated with systemic antibiotics. Rifaximin seemed to reduce the symptoms of diarrhea in patients who acquired diarrheagenic *Escherichia coli*.

In November 2018, the FDA approved another ansamycin, AEMCOLO™ (rifamycin; Aries Pharmaceuticals, Inc. [a Cosmo Pharmaceuticals N.V. Company]).[18] Like rifaximin, AEMCOLO has little systemic absorption; bioavailability is less than 0.1% according to the package insert.[19] It acts locally in the gastrointestinal tract.[20] Because the systemic absorption is minimal, there is a low likelihood of mild systemic adverse effects. AEMCOLO is unique, however, because it employs multi matrix (MMX) technology, which delivers the drug to the distal small bowel and colon.[21] The MMX delivery system is used for a few other drugs, such as the mesalamine Lialda, which acts distally, and the budesonide Uceris, which is absorbed distally. These drugs have been very effective for their indication, ulcerative colitis. Specialists in travelers' diarrhea are eager to see how the MMX technology translates into clinical use with AEMCOLO.

G&H Could you please describe the mechanism of action of AEMCOLO?

BC AEMCOLO has broad-spectrum activity against gram-negative and gram-positive bacteria.[20] It acts in the distal small intestine, where it is delivered, as well as in the colon.[22] It is approved for the treatment of diarrheagenic *E coli*, which includes the enterotoxigenic, enteroaggregative, and enteropathogenic categories.[19] These 3 pathogens are the most common causes of travelers' diarrhea, with ETEC being the most common. These pathogens are common in Mexico, the Caribbean, and many other parts of the world. They invade the small intestine. They may have some activity in the colon, and it had been thought that the upper small intestine was the area of concern. The efficacy of AEMCOLO, with its distal delivery, has suggested that these pathogens are located in distal regions as well.

G&H What trial data led to the approval of AEMCOLO for travelers' diarrhea?

BC There are 2 main studies. A study led by Dr Herbert DuPont compared AEMCOLO vs placebo for the treatment of travelers' diarrhea.[22] This phase 3 trial showed clear superiority for AEMCOLO over placebo. AEMCOLO significantly reduced the time to last unformed stool (TLUS), which was 46.0 hours in the treatment group vs 68.0 hours with placebo (P=.0008). The clinical cure rates were 81.4% in the AEMCOLO arm vs

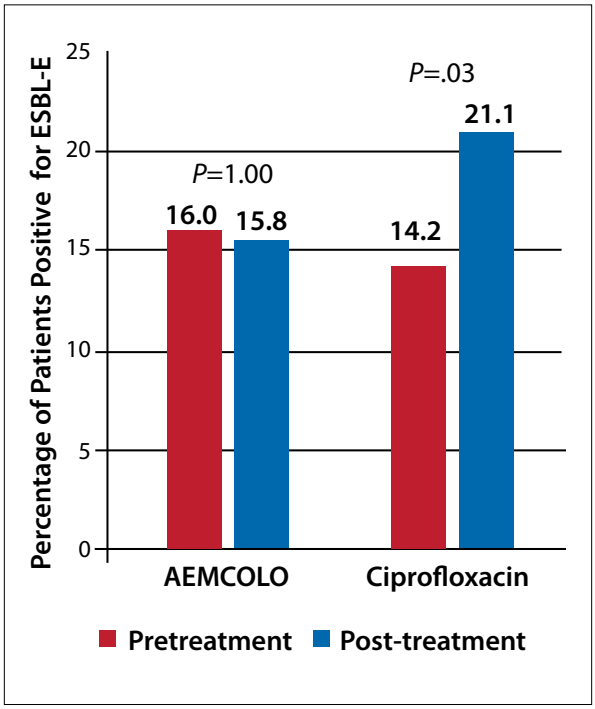

Figure 2. Rates of colonization with ESBL-E in a phase 3 trial of AEMCOLO vs ciprofloxacin. ESBL-E, extended-spectrum beta-lactamases–producing *Escherichia coli.* Adapted from Steffen R et al. *J Travel Med.* doi:/10.1093/jtm/tay116.[23]

56.9% in the placebo arm (Figure 1). AEMCOLO also decreased symptoms fairly rapidly compared with placebo. A phase 3, head-to-head study led by Dr Robert Steffen compared AEMCOLO vs ciprofloxacin in the treatment of travelers' diarrhea.[23] AEMCOLO was shown to be noninferior to ciprofloxacin, which is one of the gold standards for treatment. The median TLUS was 42.8 hours in the AEMCOLO group vs 36.8 hours in the ciprofloxacin group (*P*=.0035). This trial used a conservative definition of TLUS: the interval between the first dose of the study drug and the last unformed stool passed before the end of the clinical cure period. The results of these studies led to the FDA approval of AEMCOLO.

G&H What did the data show about AEMCOLO and ESBL bacteria?

BC An important concern with the use of antibiotics in high-risk environments is the acquisition of ESBL-producing *E coli*. Ciprofloxacin is associated with a very high rate of ESBL acquisition, as was shown in a post hoc analysis of the phase 3 trial led by Dr Steffen.[23] In the ciprofloxacin arm, colonization rates with ESBL-producing *E coli* increased by 6.9% after 3 days of treatment (Figure 2). Rates of colonization with ESBL bacteria did not increase among patients treated with AEMCOLO. If these data are confirmed in further clinical trials and postmarketing studies, they will provide an important advantage to the use of AEMCOLO.

G&H Does AEMCOLO offer any other advantages over other treatments in this area?

BC There are several advantages. AEMCOLO is minimally absorbed, so it has a low likelihood of systemic side effects.[20] The distal absorption leaves the saprophytic bacteria in the upper intestine intact. The full role of saprophytic bacteria is not known, but it is believed that maintaining homeostasis in an otherwise normal individual is a good thing.

G&H How will you use AEMCOLO in your clinical practice?

BC As a travel medicine specialist, I follow a "less is more" approach. When possible, I try not to overpower a patient with heavy-duty systemic antibiotics. I avoid drugs that will cause acquisition of multidrug-resistant bacteria. AEMCOLO is therefore a very good alternative for treatment, especially for travelers in the Western Hemisphere. AEMCOLO is not on the shelves yet, and it will be interesting to see how it is incorporated into the treatment plan. Cost is always a factor, especially for a drug treating a condition that is not life-threatening. Nonetheless, I look forward to the arrival of AEMCOLO into clinical use.

G&H Are there particular patients or settings in which AEMCOLO should not be used?

BC AEMCOLO does not treat invasive pathogens. A different antibiotic will be needed for travelers' diarrhea caused by a bacteria other than diarrheagenic *E coli*, such as *Shigella* or *Campylobacter*. There is a very high incidence of *Campylobacter* in Asia, so I would not prescribe AEMCOLO as self-treatment for travelers going there.

G&H Are there any other tips you can share about the best use of AEMCOLO?

BC Practitioners should review the literature for AEMCOLO. The arrival of any new drug is supported by plentiful information. As I mentioned, 2 pivotal trials led to the FDA approval.[22,23] Once the drug is in the clinic, there will be other studies on best use. A new project from GeoSentinel will provide insight into the use of AEM-

COLO. GeoSentinel is a network on emerging infectious disease from the International Society of Travel Medicine and the CDC. This network collects data from 75 clinics around the world that monitor ill travelers who have returned home.

G&H Are there any other diseases for which AEMCOLO shows promise?

BC An exciting aspect to AEMCOLO is that it may be effective in several other diseases. After rifaximin was approved for travelers' diarrhea and introduced into clinical use, it was quickly recognized that it could treat other conditions, such as hepatic encephalopathy, small-intestinal bacterial overgrowth, and IBS.[24] AEMCOLO, with a similar mechanism of action, may also be successful in other areas. For example, because AEMCOLO is delivered to the colon, it may prove to be an effective treatment of acute diverticulitis.[25] A nonsystemic antibiotic for acute diverticulitis would be a welcome treatment option. Even though AEMCOLO is delivered distally, it may help maintain the normal bacteria of the small bowel and could be used to treat small-intestinal bacterial overgrowth or IBS.[26] AEMCOLO may prove to be a very important addition to the field of gastroenterology.

Disclosure

Dr Connor has no real or apparent conflicts of interest to report.

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G&H