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The Growing Problem of Antimicrobial Resistance Among Enteric Pathogens

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Introduction

Traveler's diarrhea is usually caused by bacteria, and antibiotics have been successfully used to shorten the duration of the illness and facilitate the excretion of the organism.[1] Yet with each passing decade the bacteria primarily responsible for traveler's diarrhea—enterotoxigenic *Escherichia coli* (ETEC), *Shigella*, *Campylobacter*, and *Salmonella*—have become increasingly resistant to antimicrobial treatment. In the 1960s, sulfa and neomycin were being used to treat traveler's diarrhea. Tetracyclines (doxycycline) were used in the early 1970s until they were replaced by trimethoprim-sulfamethoxazole (Bactrim or Septra) in the late 1970s.[2] In the 1980s, fluoroquinolones (ciprofloxacin and norfloxacin) became standard treatment; and in the 1990s, azalides (azithromycin) began to replace fluoroquinolones.[3] All of these changes were precipitated by antimicrobial resistance to the current drug of choice. This article discusses the progression and patterns of antimicrobial resistance to the main enteric pathogens involved in traveler's diarrhea.

Etiology of Traveler's Diarrhea

In the early 1970s, ETEC was identified as a major cause of acute watery diarrhea in children living in the developing world and the major cause of traveler's diarrhea in most regions of the developing world including Asia, Africa, and Latin America.[4] Since then, studies from around the world have shown that bacterial species including ETEC and other species such as *Shigella*, *Salmonella,* and *Campylobacter* account for 50% to 60% of all cases of traveler's diarrhea. Parasites such as *Giardia*, *Cryptosporidium*, cyclospora and the viruses such as rotaviruses and caliciviruses make up the other known etiologies. No etiologic agent is found in up to 40% of cases of traveler's diarrhea. Many of these cases appear to be bacterial because they respond to antibiotics. They may be caused by a known pathogen that was undiagnosed or by some other bacterial cause that is not known or yet accepted as an etiologic agent. For example, another type of *E. coli* known as aggregative *E. coli* is currently being evaluated as another possible cause of traveler's diarrhea.[5]

Resistance among the Four Principle Causes of Traveler's Diarrhea

ETEC

Even before ETEC was discovered, it was noted that antibiotics could be used to prevent and treat traveler's diarrhea. Great Britain used sulfa compounds to prevent traveler's diarrhea in the 1968 Mexico Olympic games and to protect flight crews going to developing world airports. In 1972, when ETEC was first discovered, it was highly susceptible to all known antibiotics including those commonly used such as ampicillin, tetracycline, and sulfa.[4] ETEC were so uniformly susceptible to antibiotics that it was thought that they might be inherently susceptible by their toxin carrying capacity. However, this assumption was unfounded: as the

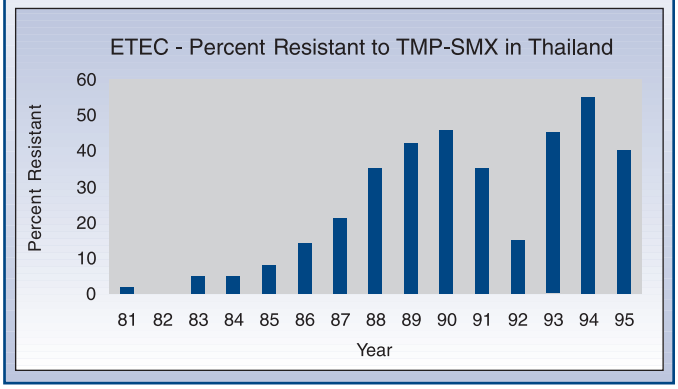
use of antibiotics spread to the developing countries, resistant organisms were soon observed.

One of the first approaches to controlling traveler's diarrhea was the use of prophylactic doxycycline. In the early studies, travelers could be protected with once daily dosing.[6] Within 10 years ETEC were no longer susceptible to the tetracyclines in many areas of the world.[7-9] The tetracyclines were replaced by trimethoprim–sulfamethoxazole (TMP-SMX) as the drug of choice. TMP-SMX is still widely used around the world and was until recently considered the drug of choice for travelers to Mexico.[10] In a study of travelers from four sites (Mombassa, Kenya; Goa, India and Montego Bay, Jamaica), TMP-SMX resistance was observed in 30% to 60% of enteric pathogens (defined as ETEC, *Salmonella,* and *Shigella*).[11,12] A follow-up study showed that enteric pathogens from Mexico had similarly high MICs and conceded that TMP-SMX can no longer be used as a first line treatment.[10,11]

The progression of TMP-SMX resistance over the last 10 years has been well documented in Thailand where the percentage of strains resistant to TMP-SMX rose from less than 5% in 1981 to over 50% by 1994 (**Figure 1**).[3] A similar pattern was observed in many parts of the world. In 1992-3, a high level of antimicrobial resistance was seen in ETEC isolated from U.S. soldiers deployed to Somalia.[13] Sixty percent (60%) to 70% of ETEC were resistant to ampicillin, doxycycline, and trimethoprim-sulfamethoxazole, all of which were rendered useless as treatment options. ETEC isolated in this study were uniformly susceptible to the fluoroquinolones.

Figure 1

Percent of ETEC isolates recovered from indigenous persons in Thailand, 1981-1995 resistant to trimethoprim-sulfamethoxazole (TMP-SMX)[3]



Ciprofloxacin was introduced in the 1980s and is one of the most widely used fluoroquinolones for the treatment of traveler's diarrhea. Because of its excellent safety profile, ciprofloxacin 500 mg twice daily for 3 to 5 days is regarded by many as the treatment of choice for traveler's diarrhea.[1,14] Until the 1990s, ETEC, *Shigella*, and *Salmonella* were entirely susceptible to the fluoroquinolones. In Thailand, none of more than 600 ETEC isolates collected from 1991 to 1993 were resistant while 2 of 241 ETEC isolated from 1994 to 1995 were resistant, with MICs > 32 ug/ml.[3] From 1994 to 1997, Vila et al. identified 5 (6%) of 82 ETEC strains as resistant to nalidixic acid and ciprofloxacin.[15] Four of the 5 strains were isolated from Spanish travelers returning from India. For all susceptible ETEC strains, the MIC_{50} was 0.012 ug/ml (**Table 1**). The MICs of the 5 resistant strains ranged from 0.03 to 32 ug/ml. Strains with a range of 0.03 to 0.25 were associated with a single mutation in the gyrA locus. The strain with the MIC of 32 ug/ml had a total of 4 point mutations in gyrA and parC. Thus, it appears that several mutations must accumulate in several select genes before resistance becomes high. Others have found that MIC_{90}s of enteropathogens isolated in India (0.25 ug/ml) were about 10-fold higher than strains isolated in Jamaica, Mexico, or Kenya.[11] This finding lends credence to Vila et al.'s study, which found ciprofloxacin resistance emerging from India.

Table 1

Mutations in the gyrA and parC genes of quinolone-resistant clinical isolates of ETEC[15]

Strain	Toxin	MIC, ug/ml		Type of Mutation and Amino Acid Change			
Designation	Type	NA	CIP	GyrA		ParC	
Wild type		3	0.01	Ser-83	Asp-87	Ser-80	Glu-84
135	ST	32	0.03	Ala			
225	ST/LT	256	0.19	Leu			
299	LT	256	0.19	Leu			
265	ST	256	0.25	Leu			
12	ST	>256	32	Leu	Asn	Ile	Gly

MIC=minimum inhibitory concentration; NA=naladixic acid; CIP=ciprofloxacin

Shigella

Shigella species are also important causes of diarrhea both among native populations in developing countries and travelers to these regions. Among the species, *S. flexneri* (group B) and *S. sonnei* (group D) are the most commonly isolated. The epidemic form of dysentery is caused by *S. dysenteriae* I (group A). In Thailand, high rates of resistance to ampicillin and TMP-SMX have been observed.[3] In the 1980s, over 80% of *Shigella* were resistant to ampicillin. In more recent years, resistance rates have fallen to about 60% in 1995 [3] and to 29% from 1996-1999.[16] Decreased use of ampicillin in Thailand may have been a factor in the decreasing the proportion of resistant strains. During the same time period (1996-1999), 77% of *Shigella* isolated in Vietnam were resistant to ampicillin. In contrast to the decreasing rates of ampicillin resistance, *Shigella* species have become increasingly resistant to TMP-SMX in Thailand.[3] Since 1988 over 90% of *Shigella* isolates from Thailand were resistant to TMP-SMX. The pattern of resistance in neighboring Vietnam is similar to that in Thailand.[16]

S. dysenteriae I, although not often a pathogen for travelers, may have different resistance patterns than *S. flexneri* or *S. sonnei*.[17] In Bangladesh, for example, 80% of the *S. dysenteriae* I isolates are resistant to ampicillin and TMP-SMX compared with about 40% of the other *Shigella*

species.[18,19] Naladixic acid and other quinolone resistance has also been more common in *S. dysenteriae* I than other *Shigella* isolates.[20]

Salmonella

Non-typhoidal *Salmonella* are generally not as resistant to antibiotics as ETEC and *Shigella*. In Thailand, *Salmonella* isolates showed the same upward trend in antimicrobial resistance but only about 28% and 37% of strains were resistant to ampicillin and TMP-SMX, respectively.[3,16] Non-typhoidal *Salmonella* were even less resistant in Vietnam where less than 10% of isolates were resistant to ampicillin or TMP-SMX (**Table 2**). All *Salmonella* strains were susceptible to ciprofloxacin and azithromycin.

Table 2

Comparative antibiotic resistance rates (%) from Vietnam and Thailand, 1996-1999[16]

	ETEC		*Shigella*		*Salmonella*		*Campylobacter*	
Antibiotic*	Thailand	Vietnam	Thailand	Vietnam	Thailand	Vietnam	Thailand	Vietnam
	n=203†	n=113	n=175	n=305	n=696	n=30	n=608	n=88
AM	54	67	29	77	28	3	nd	nd
CM	13	17	21	64	26	7	nd	nd
TMP-SMX	51	63	90	78	37	10	nd	nd
NA	3	1	1	1	21	0	73	7
CIP	2	1	0	0	1	0	77	7
TE	43	65	91	80	59	13	nd	nd
AZM	4	3	2	8	5	0	6	0

*AM=ampicillin; CM=chloramphenicol; TMP-SMX=trimethoprim-sulfamethoxazole; NA=naladixic acid; CIP=ciprofloxacin; AZM=azithromycin; ND=not done
†n=number of isolates tested

Campylobacter

Campylobacter species emerged as an important cause of diarrheal disease in the late 1970s. *Campylobacter* can be isolated in all parts of the world and is hyperendemic in many parts of the developing world. When adults with *Campylobacter* enteritis receive antibiotics to which the strain is susceptible, they improve more rapidly and they excrete the organism for a shorter time than if they did not receive antibiotics. Although *Campylobacter* can be found in all countries, it is most common in many areas of the developing world and therefore can be a common cause of traveler's diarrhea. Traveler's diarrhea caused by *Campylobacter* has been particularly common in Thailand.[21] In Thailand, an increasing resistance to tetracycline and the fluoroquinolones has been seen in the *Campylobacter* organisms.[3] A 1991 study shows that treatment with ciprofloxacin was generally efficacious for traveler's diarrhea in Thailand; however, 2 of 54 patients with *Campylobacter* enteritis had a clinical relapse after treatment with ciprofloxacin that was associated with development of ciprofloxacin resistance.[22] Ciprofloxacin resistance was documented in 40% of strains in 1993 and in over 80% of strains in 1995 (**Figure 2**). In contrast, ciprofloxacin resistance is still at low levels in Vietnam.[16]

An increase in quinolone resistance has also been documented in the United States from 1% in 1992 to 10% in 1998.[23]

The use of fluoroquinolones for growth promotion in poultry contributes to resistance in developed countries; their use in humans also contributes to resistance.[24-26] For example, the use of erythromycin in respiratory indications correlated with an increasing resistance to erythromycin in *Campylobacter* isolates. Worldwide, *Campylobacter* isolates have shown resistance to tetracycline, erythromycin, and ciprofloxacin.[27]

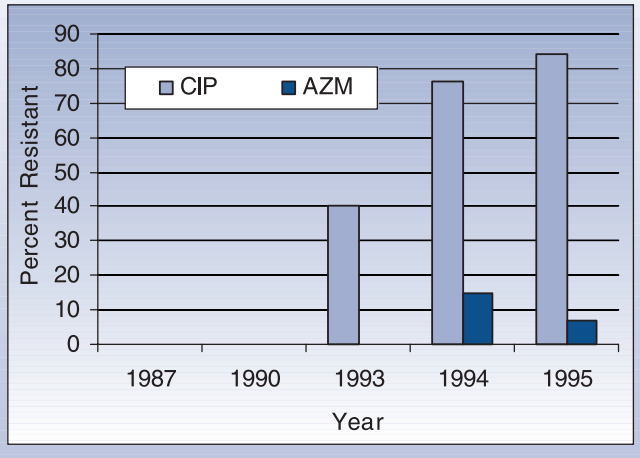
Because of the problem of ciprofloxacin-resistant *Campylobacter*, azithromycin was selected as an alternative treatment for traveler's diarrhea.[21,28,29] Azithromycin shortened the illness in a similar manner to ciprofloxacin when the isolates were susceptible to ciprofloxacin.[21] Azithromycin also eliminated the organism from the stool. Spain is another area reporting ciprofloxacin-resistant campylobacters.[28] This trend could become common, and the need for alternative antibiotics is pressing.

Conclusion

The increasing antimicrobial resistance among enteric pathogens has limited the efficacy of traditionally used antibiotics. Currently, there is a lack of reinforcements to the fluoroquinolones class of drugs. Moreover, fluoroquinolone resistance has been observed in developing countries, and the use of fluoroquinolones has not been approved for in children and women of child-bearing potential. These factors have led researchers to explore the use of non-absorbable antibiotics for the treatment of traveler's diarrhea.[30-34] Current trials in Mexico, Antigua, Guatemala, India, and Peru are expected to determine whether the minimally absorbed antibiotic rifaximin is beneficial in bacterial diarrhea. Ongoing studies will determine the value of the drug in dysenteric illness.

Figure 2

Ciprofloxacin (CIP) and azithromycin (AZM) resistance among *Campylobacter* isolates recovered from US military personnel in Thailand[3]



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Target Audience: Internists, family physicians, general practitioners, emergency department physicians, infectious diseases physicians, physician's assistants and nurse practitioners, microbiologists, and other clinicians with involvement or interest in traveler's medicine and/or antiobiotic resistance.

Learning Objectives: After reading this publication, the reader should be able to:

- List the four primary bacterial causes of traveler's diarrhea.
- For each of the four primary bacterial causes of traveler's diarrhea, discuss national and international resistance trends.

CME Self Assessment Examination

Volume VI, Issue 1

See instructions and pertinent information on the reverse before requesting credit.

1. Match the antibiotic used to treat traveler's diarrhea (Column A) with the decade in which its use emerged (Column B):

Column A (Antibiotic)	Column B (Decade)
1. Azalides	1960 _____
2. Fluoroquinolones	1970 _____
3. Sulfa/Neomycin	1980 _____
4. Tetracycline or Trimethoprim/Sulfa	1990 _____

2. Which of the following statements about traveler's diarrhea is false?

   a. 50% to 60% of traveler's diarrhea is due to ETEC, *Shigella, Salmonella*, and *Campylobacter*
   b. The etiology of traveler's diarrhea is unknown in up to 40% of cases
   c. Antibiotics have been shown to shorten the duration of traveler's diarrhea
   d. Progressive resistance to antibiotics has been shown for all pathogen classes except for ETEC
   e. None of the above

Answer _____

3. Which of the following statements about traveler's diarrhea is true?

   a. In Thailand, ampicillin resistance among *Shigella* isolates has actually decreased in the 1990s
   b. The most commonly isolated species of *Shigella* causing traveler's diarrhea are *S. sonnei* and *S. dysenteriae*
   c. *Campylobacter* causes hyperendemic infections in the developing world and is a common cause of traveler's diarrhea
   d. a and c are true
   e. None of the above

Answer _____

For questions 4-6, answer **T** if the statement is True and **F** if the statement is false.

4. _____ Fluoroquinolone use in poultry and in humans has been attributed to an increase in resistance of *Campylobacter* to fluorquinolones.
5. _____ Azithromycin is a useful alternative to treating traveler's diarrhea when resistant *Campylobacter* is of concern
6. _____ Multiple mutations in the gyrA and parC genes of ETEC seem to be associated with the highest level of naladixic acid and quinolone resistance

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