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Review

Resistant pathogens as causes of traveller's diarrhea globally and impact(s) on treatment failure and recommendations

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Abstract

Background: Diarrhea is a frequent clinical syndrome affecting international travellers. Bacterial etiologic agents have a long history of emergent antimicrobial resistance against commonly used antibiotics. Current approaches applying first-line antimicrobial therapy are being challenged by increasingly resistant organisms. This review summarizes recent epidemiological and clinical evidence of antibiotic resistance among enteropathogens causing traveller's diarrhea and the subsequent impact on current treatment recommendations.

Methods: The PubMed database was systemically searched for articles related to antibiotic susceptibility and diarrheal pathogens.

Results: Antibiotic resistance related to travellers' diarrhea has increased in recent years. Most notably, fluoroquinolone resistance has expanded from the *Campylobacter*-associated cases well documented in Southeast Asia in the 1990s to widespread occurrence, as well as increases among other common bacterial enteropathogens including, enterotoxigenic and enteroaggregative *Escherichia coli*, *Shigella* and non-typhoidal *Salmonella*. Multidrug resistance among enteropathogenic *Enterobacteriacae* and *Campylobacter* species create further challenges with the selection of empiric therapy. Treatment failures requiring early use of alternative agents, as well as delayed recovery comparable to placebo rates emphasize the impact of antimicrobial resistance on effective treatment.

Conclusions: Although there are limitations in the available data, the increasing antibiotic resistance and adverse impact on clinical outcome require continued surveillance and reconsideration of practice guidelines.

Key words: Traveller's diarrhea, antimicrobial resistance, *Campylobacter*, Enterotoxigenic *E. coli*, *Shigella*, *Salmonella*

Evolution of Antimicrobial Use in the Treatment of Traveller's Diarrhea (TD)

Diarrhea is one of the most common clinical syndromes impacting travellers, of which 80–90% of attacks are the result of bacterial pathogens (e.g., enterotoxigenic and enteroaggregative *Escherichia coli* [ETEC and EAEC, respectively], *Campylobacter* spp., *Shigella* spp. and non-typhoidal *Salmonella* spp.).[1] There are also well-recognized regional differences in the distribution of pathogens,[2] so travel destination often influences treatment recommendations. Specifically, *Campylobacter* spp. is commonly isolated from patients in Southeast Asia (particularly Thailand),[3–5] while ETEC is

frequently the causative agent for TD among travellers in the Latin America, Africa, south Asia and the Middle East.[6–9]

Although TD is a self-limited illness commonly resolving within 5 days when left untreated (quicker when antibiotics are prescribed), it frequently results in short-term morbidity adversely impacting travel plans, as well as potential for long-term enteric and extra-intestinal complications.[10] Antibiotic therapy has been proved to be effective in treating patients with TD by both significantly reducing associated symptoms and shortening the illness duration.[2,11] As antibiotic therapy remains the most effective treatment, it is common for clinicians to prescribe antibiotics to international travellers for self-treatment if they

experience diarrheal symptoms while abroad. Over the past two decades, enteropathogens have shown increasing resistance to first-line antibiotics, particularly fluoroquinolones, in endemic regions.[1,4,12–17] Decreased susceptibility of preferred antibiotics is an evolving challenge for clinicians requiring interval reconsideration of clinical practice guidelines. This review considers recent information on bacterial enteropathogen antimicrobial resistance against current first-line antibiotics, impact on clinical outcomes, and the effect on modification of clinical practice guidelines.

Factors Impacting Antimicrobial Effectiveness in TD Treatment

The effectiveness of an antibiotic to rapidly lead to clinical resolution with or without microbiological eradication is based on several factors. Randomized clinical trials provide point estimates of treatment efficacy under controlled circumstances, frequently highlighting an important subset of subjects with suboptimal (such as delayed time to resolution approximating placebo recovery rates) or outright treatment failure early in the antibiotic course or late recurrence.[18] Antibiotic selection and the relationship to enteropathogen antibiotic susceptibility alone are not the only factors impacting clinical response.

Additional considerations include host factors, such as immunocompromised states, which may decrease efficacy, as well as add risk for persistent and recurrent illness; adjunctive therapy with antimotility agents (e.g., loperamide), which is well documented to decrease duration of diarrheal episodes;[19] patient adherence to prescribed regimen; frequent co-infection challenging interpretation of attribution with resistant pathogens; and potentially non-antimicrobial effects of the therapeutic agents.[20] The clinical syndrome encompassing TD includes the most common acute watery diarrhea (AWD) presentation, in addition to dysentery or febrile AWD and even viral gastroenteritis cases that manifest with diarrhea along with the common predominance of vomiting.[1] Overall efficacy estimates for first-line therapies are reported by pooling these various clinical presentations into common TD endpoints, which tends to lose discrimination of important differences in time to recovery. Furthermore, the time of clinical presentation from illness onset is known to impact time to resolution in these self-limited illnesses.[21] Trials attempt to control for this by restricting duration of illness at time of enrolment; however, this still may fail to consider relative differences given that these illnesses can be quite short lived. Lastly, antimicrobial resistance and the effect on clinical outcomes are extremely important, but should be placed in context with the above considerations.

Current Status of Major TD Enteropathogen Antimicrobial Resistance Epidemiology

The TD bacterial enteropathogen antimicrobial resistance data derive from a number of sources, which have strengths and limitations. Direct assessment of clinical microbiology from a TD treatment trial is most likely to report the relationship of clinical outcomes relative to susceptibility. Other sources of information stem from epidemiological surveys of travellers with TD, either at the travel destination or upon return to their home country, as well as, surveys on non-travellers (e.g., children from developing worlds in their country of residence), which are often extrapolated to inform regional infection threats. Irrespective of the information source, a significant challenge in translating this information to clinical practice guidance is interpretation of the susceptibility criteria.[22] Interpretative criteria relies on clinical breakpoint development generated by standardized *in vitro* susceptibility testing, pharmacological parameters, and, importantly, clinical outcome studies, which are often lacking. Further complicating interpretation is the extremely high faecal antibiotic levels relative to a pathogen's minimum inhibitory concentration (MIC) for both systemic and non-absorbable antibiotics as follows: azithromycin with a 11–14 h half-life has ~50% active drug excreted in stool with high tissue levels,[23,24] ciprofloxacin has 100- to 1000-fold faecal levels above serum levels with 19% oral dose excreted as metabolites in faeces, as well as high tissue levels,[25] and rifaximin is <0.4% absorbed with 4000–8000 µg/g faecal levels at the 400 mg two times daily dose.[26]

The following summarizes recent reports focusing on traveller populations highlighting the continued evolution of antimicrobial resistance against first-line agents. The summary first considers the TD-causing *Enterobacteriaceae* species followed by *Campylobacter jejuni/coli*.

TD-Causing *Enterobacteriaceae*

Antibiotic resistance among enteric bacterial pathogens has been steadily increasing over the last two decades.[4,16,27–32] A recent review of EAEC epidemiology and clinical manifestations summarized the increasing rates of multidrug resistance including loss of fluoroquinolone activity as well as extended-spectrum beta-lactamase (ESBL) production.[33] Moreover, a comprehensive study assessed ETEC and EAEC isolate changing antibiotic susceptibility trends over a decade among adult travellers to Mexico, India, and Guatemala with TD.[27] The older agents, such as ampicillin, trimethoprim-sulfamethoxazole, and doxycycline, retained high levels of resistance. Fluoroquinolones and azithromycin MICs were significantly higher than when assessed 10 years prior. Regional variation in ETEC fluoroquinolone resistance was also demonstrated with higher rates in India compared with Central America. The EAEC isolates from Central America showed increased resistance across most antibiotics tested. In addition to the observed increases in fluoroquinolone resistance, 4- to 10-fold increases in MIC_{90} values for ceftriaxone and azithromycin were also seen for both ETEC and EAEC. The non-absorbable antibiotic rifaximin had no significant changes in ETEC or EAEC MICs.

In recent years, a rise in clinical resistance, often multidrug-resistance, to first-line antibiotics (e.g., fluoroquinolones and azithromycin) and alternative agents (e.g., third-generation cephalosporins) has been reported in *Shigella* spp. and *Salmonella* spp. diarrheal patients.[34–44] The past 10–15 years have seen higher rates of fluoroquinolone resistance in surveys among industrialized countries with a large proportion associated with foreign travel.[36,38,39] Multidrug resistance is also being reported, including decreased azithromycin susceptibility, ESBL production, coupled with loss of fluoroquinolone activity.[37] The strong association with quinolone resistance and foreign travel has also been reported with non-typhoidal *Salmonella* species through the US antimicrobial resistance

monitoring systems.[43] Furthermore, resistance to ciprofloxacin was reported in 20.9% of *Salmonella enterica* isolates collected in the UK and associated with treatment failure.[42] As seen in *Shigella* spp.,[40] non-typhoidal *Salmonella* also have increasing evidence in MDR strains of losing available alternative agents, such as cefotaxime.[44]

Campylobacter jejuni/coli. Although an increasing level of fluoroquinolone resistance has been reported with many enteric pathogens, there is less information connecting resistance to clinical treatment failure. Presently, the association between emergent resistance and adverse clinical outcomes is best understood with *Campylobacter* spp. (Table 1). The emergence of fluoroquinolone resistance among *C. jejuni/coli* started earlier (i.e., 1990s)[45–47] than the increasing trends over the past decade observed among diarrheagenic *E. coli*, *Shigella*, and *Salmonella* strains. Thailand has been a region with particularly rapid emergence with fluoroquinolone resistance among *Campylobacter* spp. increasing from zero in 1990 to 84% in 1995.[45] In one analysis, travellers with confirmed bacterial enteritis within one month after travel to the tropics were examined. *Campylobacter jejuni* was the etiologic agent in 41% of cases, of which 53% of isolates were resistant to norfloxacin. Clinical failure occurred in 33% of patients who were prescribed fluoroquinolines.[29] Surveillance of *Campylobacter* spp. isolates over a 10-year period (2001–10) in Peru found ciprofloxacin resistance of *C. jejuni* and *Campylobacter coli* in Lima significantly increased from 73.1 to 89.8% and 48.1 to 87.4%, respectively. Resistance of *C. jejuni* to azithromycin and erythromycin also significantly increased from 2.2 to 14.9% and 3.2 to 14.9%, respectively, in Iquitos, Peru.[31]

Among the confirmed cases of *Campylobacter* spp. infections affecting people in the United States (2005–11), 18% were associated with international travel. Data also suggest that a significant portion of fluoroquinolone resistance among *Campylobacter* spp. infections in the United States, as well as other countries,[48] may be the result of acquisition through international travel. Specifically, 60% of travel-related *Campylobacter* spp. infections were found to be fluoroquinolone-resistant, while it was only 13% of domestic cases. Macrolide resistance, which was significantly associated with an increased risk of hospitalization, was observed with 4% of travel-related *Campylobacter* spp. infections, which has been observed at similar, relatively stable, rates in other surveys.[49] In general, the majority of travel-related *Campylobacter* spp. infections resulted from travel to Asia, Mexico, or South America, and a high proportion were resistant to at least two fluoroquinolones (78, 62, and 83%, respectively).[50] Fluoroquinolone resistant *C. jejuni/coli* has now become a widespread problem among industrialized and developing countries.

Evidence of TD Enteropathogen Treatment Failure Related to Antimicrobial Resistance

Treatment response in a majority of randomized control trials utilizes the time from initial antibiotic dose to the last unformed stool (TLUS). This endpoint does correlate well with overall clinical resolution, but other important outcomes include clearance of associated symptoms along with functional recovery and return to regular activities.[18] The eradication of pre-

treatment isolates, typically days 5–9 after the last treatment day, has not correlated well with clinical outcome.[51] Early studies comparing azithromycin and ciprofloxacin in patients with shigellosis demonstrated high faecal antibiotic levels for both drugs with no evidence of resistance; however, treatment failure rates among *S. dysenteriae* type 1 were as high as 29 and 17% in the azithromycin and ciprofloxacin groups, respectively.[52] In comparison the non-*dysenteriae* shigellosis cases had overall treatment failure rates, irrespective of drug, of only 6%, suggesting impact of specific pathogen, relative severity of disease at presentation, or both.

In a randomized, double-blind treatment trial comparing azithromycin and levofloxacin regimens, military personnel presenting with acute diarrhea while serving in Thailand were enrolled. *Campylobacter* spp. were isolated from 64% of patients, of which *C. jejuni* was predominant (95%). The *Campylobacter* spp. isolates were all susceptible to azithromycin; however, 50% and 93% were resistant to levofloxacin and ciprofloxacin, respectively. The TLUS was significantly different among subjects with levofloxacin-resistant *Campylobacter*-associated diarrhea who were provided the levofloxacin regimen (76.4 h compared with 41.2 h in subjects with levofloxacin-susceptible isolates and 41–47 h in subjects receiving azithromycin; $P = 0.008$; Figure 1). Clinical cure (i.e., resolution of diarrhea and associated symptoms within 72 h) was 96% for patients receiving single dose of azithromycin and 70% for 3 days of levofloxacin.[4]

While rifaximin has been shown to be effective at treating TD, it should not be prescribed in cases of febrile invasive disease where there have been clearly documented cases of primary treatment failure.[53,54] Furthermore, rifaximin should specifically not be prescribed when *Campylobacter* is the etiologic agent due to its high level of resistance and clinical outcome evidence of treatment failure.[55] Rifaximin MICs for ETEC and EAEC have been shown to increase among cases with persistent infection; however, this has not correlated with a decline in treatment efficacy.[53]

Impact of Resistant Pathogens on Treatment Recommendations

Current clinical practice patterns have been greatly impacted by the increasing levels of antibiotic resistance over the last two decades, as well as regional differences in the profile of resistant pathogens. Specifically, increased resistance of common enteropathogens to older first-line antibiotics, in addition to currently used absorbable systemic antibiotics, created a challenging situation for clinicians leading to past modification of practice guidelines. Although there are significant limitations in the available studies with outcome data, the findings show that the presence of a resistant phenotype often results in suboptimal clinical outcomes, including treatment failure. This is particularly evident with the case of the high level of fluoroquinolone-resistant *Campylobacter* spp. isolated in Southeast Asia. Further surveillance and assessment of outcomes are needed in order to examine trends in antibiotic resistance and modify treatment regimens to rapidly achieve clinical cure while balancing safety and emergent resistance concerns.

Table 1. Antibiotic resistance of *Campylobacter jejuni/coli* and clinical implications

Region	Location	Antibiotic[a]	Source[b]	Date of isolate collection	Clinical implications[c]	Reference
Asia						
	Asia	Fluoroquinolones	Travellers	1994–2000; 2001–2006	Increased from 36% resistant to 71% resistant (statistically significant)	[49]
	Asia (excluding China)	Fluoroquinolones/ Nalidixic acid	Travellers	2005–2011	78% resistant	[50]
		Macrolides	Travellers	2005–2011	6% resistant	[50]
	East Asia	Fluoroquinolones	Travellers	1994–2000; 2001–2006	Increased from 48% resistant to 61% resistant (significance not stated)	[49]
	Southeast Asia (Thailand)	Fluoroquinolones	Travellers	1990	All pretreatment isolates susceptible to ciprofloxacin (MIC = 0.2 µg/ml) **2 patients (4%) had clinical enteritis relapse associated with development of ciprofloxacin resistance (MIC >16 µg/ml after treatment)**	[46]
			Travellers	1993	50% of isolates were resistant to ciprofloxacin (MIC $\geq$4 µg/ml) **48% recovered within 48 h** **10% clinical failure; 29% bacteriologic failure**	[47]
			Domestic	1981–1995	Significant increase from zero in 1990 to 84% resistant in 1995	[45]
			Travellers	1998	96% resistant; **MICs ranged from 4 to 64 µg/ml, but no association with treatment failure** **Sub-optimal treatment response observed in 17% of cases**	[5]
			Travellers	2000–2001	93% resistant ciprofloxacin; MIC_{50} 16 µg/ml; MIC_{90} >64 µg/ml 50% resistant to levofloxacin; MIC_{50} 6 µg/ml; MIC_{90} >64 µg/ml **38% cure rate with levofloxacin within 48 h (71% within 72 h); 13% clinical failure**	[4]
			Travellers	2000–2006	64% resistant	[29]
		Macrolides	Travellers	1993	All isolates were susceptible (MIC $\leq$2 µg/ml) **62% recovered within 48 h** **No treatment or bacteriologic failure**	[47]
			Domestic	1981–1995	7–15% resistant in 1994/1995 All isolates resistant to azithromycin were also resistant to ciprofloxacin	[45]
			Travellers	1998	No resistance	[5]
			Travellers	2000–2001	No resistance; **96% cure rate for single dose within 72 h; 96% microbiological cure**	[4]
			Travellers	2000–2006	No resistance	[29]
	China	Fluoroquinolones/ Nalixidic acid	Travellers	2005–2011	100% resistant	[50]
		Macrolides	Travellers	2005–2011	11% resistant	[50]
	Indian subcontinent	Fluoroquinolones	Travellers	1994–2000;2001–2006	Increased from 29% resistant to 79% resistant (statistically significant)	[49]
Europe and North America						
	Eastern Europe	Fluoroquinolones/ Nalidixic acid	Travellers	2005–2011	79% resistant	[50]
		Macrolides	Travellers	2005–2011	5% resistant	[50]
	Belgium	Fluoroquinolones	Domestic	1994–2000; 2001–2006	Increased from 9% resistant to 43% resistant (statistically significant)	[49]
	Western Europe	Fluoroquinolones/ Nalidixic acid	Travellers	2005–2011	50% resistant	[50]
		Macrolides	Travellers	2005–2011	1% resistant	[50]

Table 1. (continued)

Region	Location	Antibiotic[a]	Source[b]	Date of isolate collection	Clinical implications[c]	Reference
	North America (excluding United States)	Fluoroquinolones/ Nalidixic acid	Travellers	2005–2011	12% resistant	[50]
		Macrolides	Travellers	2005–2011	Zero resistance	[50]
Africa						
	Africa	Fluoroquinolones	Travellers	1994–2000; 2001–2006	Increased from 14% resistant to 32% resistant (statistically significant)	[49]
		Fluoroquinolones/ Nalidixic acid	Travellers	2005–2011	37% resistant	[50]
		Macrolides	Travellers	2005–2001	1% resistant	[50]
	Sub-Saharan Africa	Fluoroquinolones	Travellers	2000–2006	31% resistant	[29]
		Macrolides	Travellers	2000–2006	No resistance	[29]
	West Africa	Fluoroquinolones	Travellers	1994–2000; 2001–2006	Increased from 7% resistant to 29% resistant (statistically significant)	[49]
Central/Latin America and Tropics						
	Mexico	Fluoroquinolones/ Nalidixic acid	Travellers	2005–2011	62% resistant	[50]
		Macrolides	Travellers	2005–2011	4% resistant	[50]
	Central America (excludes Mexico)	Fluoroquinolones/ Nalidixic acid	Travellers	2005–2011	51% resistant	[50]
		Macrolides	Travellers	2005–2011	3% resistant	[50]
	South America	Fluoroquinolones/ Nalidixic acid	Travellers	2005–2011	83% resistant	[50]
		Macrolides	Travellers	2005–2011	4% resistant	[50]
	Peru	Fluoroquinolones	Domestic	2001–2006; 2006–2010	Significantly increased in Lima from 73% resistance to 90% for *C. jejuni* Significant increase of 48% resistance to 87% for *C. coli*	[31]
		Macrolides	Domestic	2001–2006; 2006–2010	Significantly increased in Iquitos from 2% azithromycin resistance to 15% for *C. jejuni* Significant increase of 3% erythromycin resistance to 15% for *C. jejuni*; 15% of isolates resistant to both azithromycin/erythromycin and ciprofloxacin in Iquitos in 2006–2010	[31]
	Caribbean and Central/ South America	Fluoroquinolones	Travellers	1994–2000; 2001–2006	Increased from 28% resistant to 61% resistant (statistically significant)	[49]
	Combined tropics	Fluoroquinolones	Travellers	2000–2006	**33% clinical failure**	[29]
			Travellers	2002–2003	MIC >0.25 µg/ml in 42% of isolates	[53]
		Rifaximin	Travellers	2002–2003	Pre-treatment: MIC ranged 0.06–0.5 µg/ml; Post-treatment: MIC ranged 0.06–0.125 µg/ml	[53]

[a]Antibiotics used in the studies are classified as fluoroquinolones, macrolides, and rifaximin. Macrolides includes azithromycin and erythromycin. Fluoroquinolones include norfloxacin, levofloxacin, and ciprofloxacin.

[b]Source indicates whether isolates were collected from travellers or residents of the location (domestic).

[c]Bolded text in clinical implications column indicates reported clinical outcomes.

Conflict of interest

The views expressed are those of the authors and does not necessarily reflect the official views of the Uniformed Services University of the Health Sciences, National Institute of Health or the Department of Health and
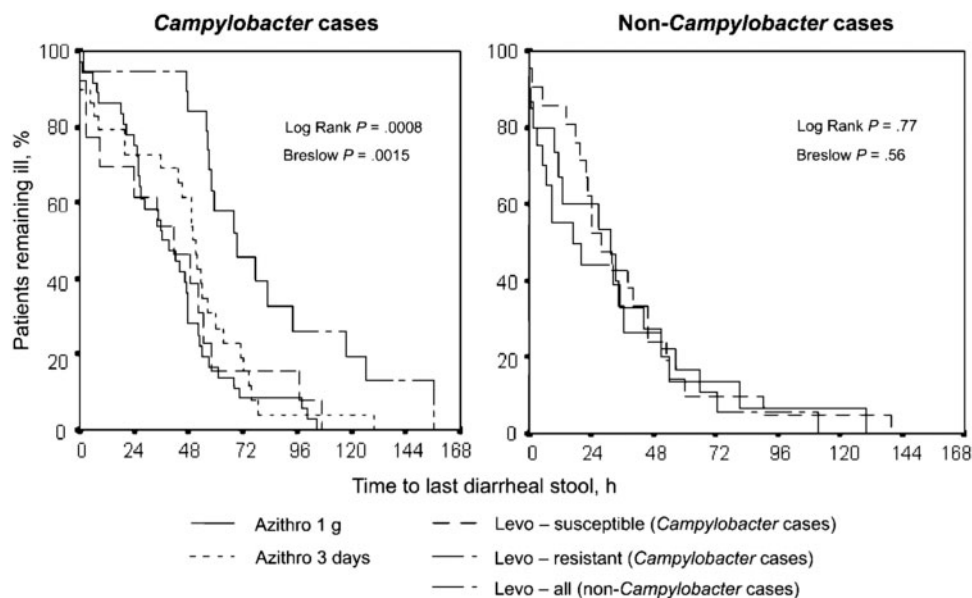
Figure 1. Time to cure (after receipt of the first antibiotic dose), by treatment group, as stratified by diagnosis of Campylobacter infection. This figure has been reprinted from Tribble *et al.*[4] by permission of Oxford University Press.

Human Services, the Department of Defense or the Departments of the Army, Navy or Air Force. Mention of trade names, commercial products, or organization does not imply endorsement by the U.S. Government.

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