

Antimicrobial Stewardship and the Treatment of Travelers' Diarrhea: Is it Time to Re-think Recommendations?

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Abstract: Diarrhea is common among those visiting developing countries and is the most frequent travel related illness. Multiple guidelines suggest travelers' diarrhea should be treated with antimicrobials. Self-treatment with antibiotics has been shown to shorten illness by 1–2 days but not without the potential risk of side effects. This treatment also needs to be balanced with the impact of antimicrobial pressure on the generation of resistance. In the era of antimicrobial stewardship, and with increasing global resistance among many different pathogens including those causing travelers' diarrhea, perhaps the recommendations for self-treatment should be re-examined. In this review we will examine the question; is the modest improvement in symptoms in an otherwise self-limiting illness worth the antimicrobial pressure?

Keywords: travelers' diarrhea, treatment, resistance, antimicrobial stewardship

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Introduction

Diarrhea is common among those visiting developing countries and is the most frequent travel related illness.¹ It is estimated that over 100 million people from industrialized nations travel to developing countries annually, resulting in up to 40 million cases of travelers' diarrhea each year.^{1,2} Travelers' diarrhea is defined as three or more unformed stools per 24 hours plus a sign or symptom of an enteric infection. It is usually self-limiting, but can lead to disrupting travel and may result in persistent symptoms in a minority of patients.^{1,3} As outlined in Table 1, bacterial, viral and protozoal pathogens may cause travelers' diarrhea.⁴

An evolving standard of care in the treatment of traveler's diarrhea has been an emphasis on self-initiated therapy without physician consultation.⁵ Multiple guidelines suggest travelers' diarrhea should be treated with antimicrobials.^{4,6,7} Self-treatment with antibiotics has been shown to improve illness within a few days of initiating therapy and shorten illness by 1–2 days but not without the potential risk of side effects.⁸ This treatment also needs to be balanced with the impact of antimicrobial pressure on the generation of resistance. Ampicillin, doxycycline, and trimethoprim-sulfamethoxazole were treatment options for travelers' diarrhea, but due to high resistance levels, these drugs are no longer effective.^{3,9–12} In fact, there are more fluoroquinolone resistant strains of *Campylobacter* than there are susceptible strains in many regions of the world.²

In the era of antimicrobial stewardship (Table 2)¹³, and with the increasing global resistance among many different pathogens including those causing travelers' diarrhea, perhaps the recommendations for

Table 1. Causes of Travelers' Diarrhea.⁴

Enterotoxigenic <i>Escherichia coli</i>
<i>Campylobacter jejuni</i>
Other <i>E. coli</i>
<i>Shigella</i> spp
<i>Salmonella</i> spp.
<i>Aeromonas</i> spp.
<i>Plesiomonas</i> spp.
Viral*
Protozoal**

Notes: *Viral including norovirus, rotavirus, and astrovirus; **Protozoal including *Giardia*, *Entamoeba histolytica*, *Cryptosporidium*, *Cyclospora* and *Dientamoeba fragilis*.

Table 2. Spectrum and Goals of Antimicrobial Stewardship.¹³

Spectrum

Limiting inappropriate use of antibiotics.
Optimizing selection, dosing, route, and duration of antimicrobial therapy.

Goals

Maximizing clinical cure or prevention.
Limiting consequences (eg, emergence of resistance, adverse drug reactions, cost).

self-treatment should be re-examined. In this review we will examine the data on the efficacy of treatment for travelers' diarrhea, antimicrobial resistance in pathogens that cause travelers' diarrhea and potential alternatives to antimicrobial therapy to address the question; is the modest improvement in symptoms in an otherwise self-limiting illness worth the antimicrobial pressure?

Search Strategy

A systematic search of the literature was completed in November 2011. Search terms used included "travel\$" or "travel*" for traveler's, traveler's, or travelers', and "diarrhea" or "diarrhoea". Two databases were searched, including MEDLINE (from 1966 to November 2011) and the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 10, October 2011). All randomized controlled trials (RCTs), meta-analyses, and systematic reviews that assessed the antimicrobial treatment of travelers' diarrhea with antimicrobial therapy were extracted for assessment. In addition, references lists of identified studies were reviewed to identify additional trials. A 2003 systematic review was retrieved that included the majority of RCTs identified in the search strategy.⁸ Three randomized controlled trials were identified that were published after the search date of the 2003 review, and were also included.^{14–16}

Treatment of Travelers' Diarrhea

A 2003 Cochrane systematic review assessed the impact of treatment with antimicrobials in 20 RCTs.⁸ Antimicrobials evaluated in the trials in the systematic review included fluoroquinolones, azithromycin, and poorly-absorbed antibiotics including rifaximin, aminoglycosides, and aztreonam. Dosing regimens varied between trials, ranged from single-dose



regimens to 5 days, and adjunctive therapies such as loperamide.

Study quality was limited and inconsistencies in methodologies between trials were noted.⁸ Twelve of these trials were placebo-controlled. Mean duration of unformed stools were available in six trials. Unfortunately, data were not sufficient to combine into a meta-analysis, but statistically significant reductions in time to last unformed stool were seen in all but one trial. Overall, the odds of being cured at 72 hours were higher in the treated groups (OR 5.94); however, the duration of diarrhea in the treatment groups was only reduced by approximately 1.5 days compared to placebo (53.6 to 60 hours vs. 24.8 to 26 hours). Only two trials reported data on the severity of diarrhea, with modest reductions in frequency of stools. For the first 24 hours, 25–48 hours, and 49–72 hours post-randomization, stools were reduced by 1.59 (95% CI –2.66 to 0.52), 2.10 (95% CI –2.78 to –1.42), and 1.38 stools (95% CI –1.94 to –0.82), respectively. Results were only statistically significant on days two and three post randomization.

Aggregate data from five trials illustrated that the marginal reduction in severity of diarrhea was offset by a more than doubled odds of adverse effects; odds ratio of 2.37 (95% CI 1.50 to 3.75).⁸ Adverse effects were generally not severe and resolved with discontinuation of the drug. Data regarding occurrence of *Clostridium difficile* infection (CDI) in patients with recurrent diarrhea were not reported.

Placebo-controlled trials published since 2003 have evaluated the efficacy of the poorly-absorbed rifaximin, an antimicrobial not yet commercially available in many countries.^{14–16} These trials, like those included in the systematic review, are of moderate quality based on Jadad scores of 3 to 4.¹⁷ A trial in 380 travelers to Antigua, Guatemala, Mexico, and Kenya treated with rifaximin reduced the duration of diarrhea by approximately 27 hours compared to placebo.¹⁴ There was no difference between the standard (200 mg three times daily) and higher dose (400 mg three times daily) treatment arms. The impact on severity, as measured by frequency of unformed stools, was marginal yet statistically significant, and similar between doses (mean 3.8, 2.6, and 0.9 stools vs. 3.1, 1.6, and 0.5 stools on days 1, 2, and 3 for placebo and rifaximin arms, respectively).

In a study of 311 students from the United States attending school in Mexico, the median time to last unformed stool was reduced in those receiving rifaximin or rifaximin and loperamide compared to loperamide alone (32.5 hours, 27.3 hours and 69.0 hours respectively).¹⁵ Clinical cure (defined as time to last unformed stool of less than 120 hours) occurred more frequently with rifaximin treatment versus loperamide, OR 1.76 (95% CI, 1.26–4.70). However, severity of disease, as measured by median number of loose stools, was only reduced when the combination of the two drugs was administered with the loperamide-containing treatment arms experiencing fewer loose stools within the first 24 hours when compared with rifaximin alone. Overall rates of adverse effects were similar between groups, although the loperamide monotherapy arm experienced more abdominal pain and vomiting than the rifaximin arms.

A multicentre trial comparing rifaximin to ciprofloxacin and placebo in 399 travelers visiting clinics in India, Mexico, Guatemala, or Peru found similar results.¹⁶ Both ciprofloxacin and rifaximin reduced diarrhea by approximately 1 day (from 65.5 hours to 28.8 hours and 32.0 hours, respectively). Although statistically significant, the α thresholds for significance do not appear to be adjusted to account for multiple comparisons, limiting the validity of results. What is most concerning is the evolution of resistance in treated patients. Although only 19 of 71 patients had persistent enterotoxigenic *Escherichia coli* (ETEC) after treatment, 10 had a 4-fold increase in the minimum inhibitory concentration (MIC) of rifaximin post-treatment. While this has little effect on clinical response because the intraluminal concentrations of the drug is 1000 fold higher than the MIC, this is one of the few studies that establishes the risk of the development of resistance with empiric treatment of travelers' diarrhea. In a subgroup analysis, while time to last unformed stool was similar in groups with higher baseline MICs, eradication rates were lower.

As empiric therapy, all studied regimens have similar efficacy in reducing duration of symptoms. However, differences in efficacy between antimicrobials exist when local resistance is high. For example, in areas with high rates of fluoroquinolone resistant *Campylobacter*, single-dose azithromycin has been



demonstrated to be an acceptable alternative and is associated with statistically significantly fewer treatment and microbiologic failures.¹⁸

Overall, results from RCTs are limited by methodological flaws, including improper statistical comparisons. The authors of the 2003 Cochrane Review identified most trials to be of poor quality.⁸ As most primary outcomes are defined by the time to unformed stools, survival analysis should be applied for statistical comparisons of treatment arms. In addition, reported results from trials are often limited to the short term (often less than one week) limiting interpretations of the efficacy of antimicrobial treatment in the prevention of long-term sequelae including residual symptoms which can persist for several weeks after initial infection. Few trials assess the impact of antimicrobial therapy on resistance, and lack sufficient sample sizes to determine the effect of antimicrobial therapy on infrequent complications of travelers' diarrhea. The available trials also do not consistently or comprehensively report the occurrence of adverse effects of antimicrobial therapy, including infectious complications such as CDI. Despite these limitations, trials have shown antimicrobial therapy is associated with a 1 to 2 day reduction in time to last unformed stool. Stool frequency, also statistically significantly reduced in published trials, is generally reduced by 2 or less loose stools per day.^{8,14-16} This small reduction in severity of symptoms is of questionable clinical significance, and is associated with an increased risk of antimicrobial resistance and adverse effects. The effect of antimicrobial therapy on the infrequent complications and long-term sequelae of travelers' diarrhea is not well described.

Antimicrobial Risks and Resistance

Like any medication, potential risks to the use of antimicrobials need to be considered before initiating treatment.

Fluoroquinolones and macrolides, the most common classes of drugs recommended for the treatment of travelers' diarrhea, are generally well tolerated. Most adverse events including gastrointestinal side effects may overlap with travelers' diarrhea symptomatology. In fact, both macrolides and particularly fluoroquinolones are associated with causing diarrhea including CDI.¹⁹⁻²² More severe

fluoroquinolone side effects including anaphylactic reactions, Stevens-Johnson Syndrome and Achilles tendon rupture are rare. Specifically, one study not related to travelers' diarrhea has shown that anaphylactic reaction and Achilles tendonitis/rupture occurred in 1 and 5 patients respectively out of a total 110 reported adverse drug reactions to ciprofloxacin.²³ Also a study from Thailand evaluating adverse drug reactions to fluoroquinolones has reported that Steven-Johnson Syndrome and anaphylactic reactions occurred in 14 and 7 patients, respectively, out of 151 patients included in the study with adverse drug reactions.²⁴

The potential for interactions with other medications needs to be considered before initiating treatment for travelers' diarrhea. Macrolides and fluoroquinolones may prolong the QT interval which can rarely lead to torsades de pointes and possibly death.²⁵ In addition, macrolides inhibit the CYP450 system, which may increase the concentration of certain common drugs including statins and subsequently increase the risk of development of rhabdomyolysis.²⁵

Although controversial, there are data to suggest that antimicrobial treatment in patients with *E. coli* O157:H7 infection may put the patient at risk of hemolytic-uremic syndrome.²⁶ Although these invasive pathogens are uncommon causes of travelers' diarrhea, they do occur and inadvertent therapy may worsen the outcome.

Perhaps the most significant risk of antimicrobial treatment is the generation of resistant organisms. The use of antibiotics can lead to the selective pressure that allows for the colonization and overgrowth of other potential pathogens including *C. albicans* and development of CDI, particularly with fluoroquinolones. In addition, fluoroquinolones may select for resistant gram-positive organisms, particularly methicillin-resistant *Staphylococcus aureus*.^{22,27}

While often overlooked, resistance not only impacts the individual but can have broader implications. Resistance to broad-spectrum antimicrobials such as third generation cephalosporins and fluoroquinolones has been increasing globally. In addition, the incidence of extended spectrum beta-lactamase (ESBL) producing microorganisms and carbapenem-intermediate or resistant



Enterobacteriaceae infections has recently been rising in healthcare settings worldwide including the emergence of novel carbapenamases like New Delhi metallo-beta-lactamase (NDM's).^{28–34}

Resistance is also becoming an increasing problem with the enteric pathogens related to travelers' diarrhea. Many of these isolates show high rates of resistance to antibiotics used previously to treat travelers' diarrhea including doxycycline, tetracycline, trimethoprim/sulfamethoxazole, and ampicillin.^{9–12} Many regions are now showing increasing rates of resistance to macrolides and fluoroquinolones, the preferred agents currently recommended for empiric treatment (Tables 3 and 4).^{9,10,35}

Extended spectrum beta-lactamase (ESBLs) have also been isolated from travel related diarrheagenic *E. coli*. In a recent study from Spain 9.8% of Enteroggregative *E. coli* isolates from travelers to a developing country had ESBLs. The isolated ESBLs were also ciprofloxacin resistant and either azithromycin resistant or intermediate.³⁶

As resistance rates continue to increase, the efficacy of current recommended treatment will likely decrease. An even more important question is how does the antibiotic pressure that results from this treatment strategy impact the resistance rates of other non-diarrheal pathogens. There is a plethora of data showing that the rates of fluoroquinolone resistance to *S. pneumoniae* rates have increased over the last decade.^{37–42} While the scientific community might argue that the antibiotic pressure driving this resistance is unlikely to be from the treatment of travelers' diarrhea, the continued evolution of antimicrobial resistance and the shrinking armamentarium of effective antimicrobials should be a reminder to carefully consider whether treatment of self-limiting

illnesses are necessary and whether there are other non-pharmaceutical interventions.

Decision to Treat

Recommendations from the Canadian Committee to Advise on Tropical Medicine and Travel and United States Center for Disease Control and Prevention suggest to treat moderate-to-severe cases of travelers' diarrhea with fluoroquinolones or azithromycin in addition to supportive measures.^{4,6}

When deciding to initiate antimicrobial therapy in addition to supportive care measures, the disease burden must be considered. Travelers' diarrhea occurs frequently, but consequences are generally limited to discomfort and time away from planned vacation activities.^{43–45} The most concerning consequence of acute travelers' diarrhea is the risk of dehydration and electrolyte depletion, particularly with more severe cases.⁴³ The infection will normally resolve without intervention, and antimicrobials have been shown to modestly reduce the duration of symptoms but only have a marginal impact on symptom severity. Only about 3 to 10% of patients experience symptoms for longer than 2 weeks, and approximately 3% of patients will have symptoms that persist greater than 30 days.⁴⁴ Persistent symptoms may be due to ongoing infection, coinfection, temporary postinfection phenomena, malabsorptive syndromes, or a post-infectious irritable bowel syndrome.⁴⁴ In addition, invasive pathogens, such as *Shigella*, *Campylobacter*, and *Salmonella*, can induce immune mediated complications such as Reiter's syndrome, reactive arthritis, and exacerbate inflammatory bowel disease.⁴³ Given the short duration of trial follow-up in most antimicrobial trials for travelers' diarrhea, it is unknown the impact of antimicrobial therapy on these outcomes,

Table 3. Resistance rates in ETEC and enteroaggregative *E. coli* (EAEC) to antibiotics used to treat travelers diarrhea.⁹

Antibiotic	ETEC		Mexico and Guatemala ⁹		EAEC	
	India ⁹		N = 270		Mexico and Guatemala ⁹	
	N = 98		N = 270		N = 20	
	Resistance	Year	Resistance	Year	Resistance	Year
AMP	49.4%	2006–2008	52.8%	2006–2008	60%	2006–2008
TMPSMX	58.9%	2006–2008	46%	2006–2008	65%	2006–2008
CIP	27.8%	2006–2008	17.5%	2006–2008	35%	2006–2008
AZM	24.5%	2006–2008	16.1%	2006–2008	40%	2006–2008

Abbreviations: N, number of isolates; AMP, Ampicillin; TMP/SMX, trimethoprim/sulfamethoxazole; CIP, ciprofloxacin; AZM, azithromycin.

**Table 4.** Resistance rates in campylobacter to antibiotics used to treat travelers diarrhea.^{9,10,35}

Antibiotic	Campylobacter					
	India ¹⁰		Thailand ³⁵		Mexico and Guatemala ⁹	
	N = 72		N = 312		N = 6	
	Resistance	Year	Resistance	Year	Resistance	Year
AMP	15%	2001–2003	29%	2001–2003	0%	2006–2008
T/S	68%	2001–2003	58%	2001–2003	0%	2006–2008
CIP	71%	2001–2003	93%	2001–2003	0%	2006–2008
AZM	0%	2001–2003	<1%	2001–2003	0%	2006–2008

Abbreviations: N, number of isolates; AMP, Ampicillin; TMP/SMX, trimethoprim/sulfamethoxazole; CIP, ciprofloxacin; AZM, azithromycin.

especially given that eradication of the causative pathogen is often not seen, particularly if MICs are higher.¹⁶

The large body of evidence that exists for travelers' diarrhea is mostly limited to a younger and otherwise healthy population. It is largely unknown whether high risk populations should receive antimicrobial therapy. Given that populations at higher risk of acquiring travelers' diarrhea such as those with pre-existing gastrointestinal disorders or the Immunocompromised are also at risk of its complications, it is reasonable to extrapolate evidence to this population and treat moderate-to-severe cases of travelers' diarrhea with antimicrobials.

While rifaximin likely has a lower risk of adverse effects as it is poorly absorbed, its unavailability in some countries limits its use. Alternatives available including fluoroquinolones and azithromycin, and as discussed above, are not benign and in fact may carry significant risks.

Despite guidelines recommending treatment, there are data to suggest that actual antibiotic use in travelers is relatively low. A recent study from the Netherlands found that although travelers' diarrhea is common (597/1202 experienced travelers' diarrhea), severity was mild, and only 36 of 781 (5%) participants used antibiotics.⁴⁶ This may be due to the fact that guidelines from the Netherlands suggest treatment of travelers' diarrhea only when there is persistent high fever, dysentery or if the traveler is immunocompromised.⁴⁷ A Canadian study found similar results.⁴⁸ While 40% of 102 travelers from Calgary, Alberta, travelling to Mexico received information on travelers' diarrhea, only 11/92 travelers carried an antibiotic with them.

Alternatives to Antimicrobial Therapy

There is an old saying that an ounce of prevention is worth a pound of cure. Unfortunately there is little data examining precautions to prevent the acquisition of pathogens associated with travelers' diarrhea (Table 5).⁷ A Cochrane review has shown that hand washing can reduce the risk of diarrhea by one third in both high and low income settings.⁴⁹ Intuitively, strict food, water and hygiene precautions should decrease the risk of travelers' diarrhea as it is acquired through ingestion of contaminated food and water. However there is little evidence to support these precautions as multiple studies have shown no relation between food practices and risk of traveler's diarrhea and that the risk seems to be more related to the overall sanitation level at the travel destination.^{50–51}

Probiotics may provide an alternative route to preventing travelers' diarrhea. They are dietary supplements of living bacteria or yeast that provide their health benefits through colonization of the intestines. Several

Table 5. Proposed measures to prevent travelers diarrhea.⁷

Things to avoid

- Undercooked meat, fish and seafood
- Dairy products
- Tap water and ice cubes
- Cold sauces and toppings
- Ground grown leafy greens, vegetables and fruits
- Cooked foods that have stood at room temperature in warm environments
- Food from street vendors, unless freshly prepared and served hot

Hygiene

- Boil water or treat with either chlorine or iodine and filter with a 1 µm filter or less before use
- Wash or clean hands before eating and after using toilets

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Lactobacillus species have been studied as chemoprophylactic agents in the prevention of travelers' diarrhea. *Lactobacillus* GG in particular has shown to provide some degree of protection; however more studies are needed to provide the optimal dosing regimen.⁵¹

Vaccination is an attractive strategy to prevent infections with pathogens causing travelers' diarrhea however; current vaccination strategies against travelers' diarrhea are limited. Most focus on ETEC, the most common cause of travelers' where there is epidemiologic evidence to support the effect and role of immunity after ETEC infections and the possibility of protection by vaccines (Table 6).^{2,52}

One current vaccine option is Dukoral, which is an oral cholera vaccine that combines inactivated whole *Vibrio cholerae* with recombinant cholerae toxin B. This vaccine cross-reacts with the B subunits of the heat labile toxin (LTB) of ETEC.⁵² Unfortunately there are inconsistencies in the evidence regarding the vaccine and its use for prevention of travel related diarrhea. In a randomized double-blind field trial among rural Bangladeshi children and woman the cholera toxin BS/Whole Cell (Bs-WC) oral vaccine was found to provide short-term protection against ETEC diarrhea, as it showed 67% protection in the first 3 months following receipt of the vaccine.⁵³ One retrospective cohort study demonstrated that the incidence and duration of diarrhea was significantly lower among vaccinated than non-vaccinated travelers with an absolute risk reduction of 17%.⁵⁴ A number of additional studies have shown limited efficacy of oral cholera vaccine in preventing travelers' diarrhea. It has been estimated that approximately 7% of cases of TD could be prevented by the use of the Dukoral vaccine.⁵⁵

Another vaccine approach targeting ETEC specifically that uses a skin patch containing heat labile toxin (LT) for ETEC has shown mixed results. A double blinded placebo controlled trial failed to

demonstrate protection in recipients against developing moderate to severe diarrhea.⁵⁶ However, in a phase II trial conducted among travelers to Mexico and Guatemala, the patch provided greater than 70% protection against moderate and severe diarrhea. Participants were vaccinated before travel, with two patches (each worn for 5–8 hours) given 2 to 3 weeks apart. There was less reported diarrhea in the vaccinated compared to the placebo control group (15% vs. 22%) and the rate of moderate to severe diarrhea was higher in the placebo group (21% vs. 5%) with a protective efficacy of 75%. The study also showed overall the vaccine was safe and well tolerated with most adverse events being mild.⁵⁷

More recently an oral live attenuated vaccine consisting of three ETEC strains has been developed and is in early clinical trials. In the Phase I trial, subjects were randomized to placebo or vaccine (either low dose or high dose). There were no immediate post-vaccination reactions and no serious adverse events were observed. Non-serious side effects occurred with similar frequency across the different groups of the study, except gastrointestinal symptoms. There was an increase in frequency of gastrointestinal symptoms in the high dose group, but most of them were mild and all were self-limited. The recent phase one trial has shown tolerance and significant immunogenicity. Immunogenicity was estimated by monitoring the systemic and mucosal antibody response against colonization factors and the non-toxic B-subunits of the ETEC heat labile toxin (LT-B).⁵⁸

Conclusion

In an era of antimicrobial stewardship, given the risk of adverse events associated with antibiotics and risk of contributing to an already problematic increase in fluoroquinolone and macrolide resistance, treatment of otherwise healthy individuals for whom the duration of illness is only shortened by a few days should be limited. This has been echoed by others.⁵⁹ We could not find any data regarding the efficacy of treating travelers' diarrhea in immunocompromised hosts. However, believe that the approach adopted by the Netherlands focusing on empiric treatment for those travelers who are immunocompromised or have prolonged fever or severe diarrhea is the more prudent approach.⁴⁷ Emphasis should be more towards preventative strategies with effort and focus directed

Table 6. Epidemiologic observations supporting effect and role of immunity after ETEC infections.^{2,52}

Prevalence declines with age in endemic countries
Incidence is decreased when individuals from high risk areas visit other high risk areas
Incidence declines with prolonged stay in travelers from industrialized to developing countries



towards the development of effective and preventative vaccines.

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Author Contributions

Conceived and designed the review: KB, BRM, TFH. Analysed the data: KB, BRM. Wrote the first draft of the manuscript: KB, BRM. Contributed to the writing of the manuscript: KB, BRM, KLS, TFH. Agree with manuscript results and conclusions: KB, BRM, KLS, TFH. Jointly developed the structure and arguments for the paper: KB, BRM, KLS, TFH. Made critical revisions and approved final version: KB, BRM, KLS, TFH. All authors reviewed and approved of the final manuscript.

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