



# Acid Suppression with H2 blockers and Proton Pump Inhibitors (PPIs) is not Associated with an Increased Risk of Traveler's Diarrhea (TD)

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Abstract #58982  
Presentation # 611

## Abstract

**Background:** Gastric acid plays an important role in eliminating bacterial pathogens; agents that suppress gastric acid production such as proton pump inhibitors have been associated with infectious gastroenteritis. Achlorhydria is associated with TD, and it is speculated that those on PPIs and H2 blockers are at an increased risk, however, studies specifically examining this question are lacking. This study aims to bridge this gap.

**Methods:** The TravMil study is a cohort study that prospectively assesses infectious disease risk and effectiveness of prevention and treatment strategies among Department of Defense beneficiaries. Participants receive pre- and post-travel surveys (assessing TD symptoms and use of PPI and H2blockers se). TD was defined as 3 or more loose stools within 24 hours or 2 loose stools plus an associated symptom within 24 hours. A multivariate Poisson regression analysis was performed to examine the influence of PPI and H2 blocker use and TD.

**Results:** Of the 2,531 eligible subjects, 524 (21%) met criteria for TD. 395 (16%) subjects reported H2 or PPI blocker use. Rate of TD were similar among users 94 (24%) and non-users 430 (20%). As shown below, in a multivariate analysis, the only risk factors associated with TD were food source (street vendor) and consuming raw foods. Use of PPIs and H2 blockers were not associated with TD even in the univariate analysis [RR: 1.18 (0.97-1.44)]. Regional travel and military purpose were not significant in the univariate analysis.

**Conclusion:** in our cohort self-reported use of PPIs/H2 blockers were not associated with TD. We confirmed several previously identified risk factors for TD. These results suggest that no additional counseling over the standard regimen may be needed for patients on a PPI or H2 blocker, but our results need confirmation in larger cohorts.

## Study Rationale

- Pre-administration of sodium bicarbonate was shown to reduce the required inoculum of E. coli needed to cause infection in human volunteers.<sup>1</sup> This suggests that stomach acid is an important barrier to certain types of infection.
- Several case control trials have shown an increased risk of Salmonellosis and Campylobacter infection with use of acid suppressive(AS) medication.<sup>2,4</sup>
- A large Dutch cohort of 743 travelers observed an OR of 5.22; 95%CI (0.62-43.83) for developing TD on any antacid therapy but failed to demonstrate significance due to the small sample size.<sup>3</sup>
- The expert guidelines for the prevention of TD published in 2009 recommend considering chemoprophylaxis for travelers with reduced gastric acid by drugs, or diseases<sup>4</sup>.
- There is strong physiologic plausibility and indirect evidence that supports the hypothesis that AS may increase the risk for developing TD, hence we explored this association in our cohort.

Table 1. Demographics of travelers using Acid Suppression AS

Who is on Acid suppression (AS)	Did Not Use AS N(%)	Used AS N(%)	Univariate RR(95%CI)
<b>Age</b>			
≤24 years	352(97.5)	9(2.5)	Ref.
25-50 years	935(89.3)	112(10.7)	<b>4.29(2.20-8.40)</b>
≥ 50 years	849(75.6)	274(24.4)	<b>9.78(5.09-18.81)</b>
<b>Gender</b>			
Male	1188(83.6)	233(16.4)	Ref.
Female	947(85.4)	162(14.6)	0.89(0.74-1.07)
<b>Race</b>			
White	1514(84.0)	290(16.0)	Ref.
Asian	172(77.1)	51(22.8)	<b>1.42(1.05-1.92)</b>
Black/African American	241(91.6)	22(8.4)	<b>0.52(0.34-0.80)</b>
Other Race	202(87.0)	30(12.9)	0.80(0.55-1.17)

Table 2. Severity and number of stools by use of AS

Risk and Severity of TD	Did Not Use AS N(%)	Used AS N(%)	Univariate RR(95%CI)
Did not develop TD	1706(85.0)	301(15.0)	Ref.
Developed TD	430(82.0)	94(17.9)	1.19(0.96-1.47)
Mild TD	200(83.3)	40(16.6)	Ref.
Moderate/Severe TD	229(81.8)	51(18.2)	1.16(0.82-1.62)
2-5 loose stools	321(82.7)	67(17.3)	Ref.
≥ 6 loose stools	24(77.4)	7(22.6)	1.30(0.66-2.60)

## Results

Table 3. General risk factors for TD

Risk Factors for TD	Univariate RR(95%CI)	Multivariate RR(95%CI)
Gender		
Female	<b>1.22(1.05-1.42)</b>	1.14(0.98-1.34)
Antibiotics Use		
Doxycycline	<b>0.75(0.58-0.96)</b>	0.82(0.65-1.04)
Food Source		
Street Vendor	<b>1.40(1.18-1.68)</b>	<b>1.49(1.23-1.80)</b>
Drink untreated water	<b>1.70(1.43-2.00)</b>	1.06(0.86-1.32)
Using Ice	<b>1.26(1.08-1.48)</b>	0.98(0.83-1.17)
Consumption of Raw Food	<b>1.71(1.47-2.00)</b>	<b>1.51(1.29-1.77)</b>

Table 4. Risk Risk of AS for TD under the Age of 50

	RR for Subjects under the age of 50		
	Developed TD	No TD	Totals
Used AS	46	75	121
Did not use any AS	268	1019	1287
Totals	314	1094	1408
Relative Risk	<b>1.82</b>	<b>CI: 1.42-2.34</b>	

## Methods

- TravMil is a cohort study that prospectively assesses infectious disease risk and effectiveness of prevention among Department of Defense beneficiaries who visited 5 military travel clinics for counseling between January 2010 and March 2016
- Travelers included in the cohort traveled outside of the US for ≤6.5 months
- Travelers to Northern Europe, Canada, or New Zealand were excluded
- TD and AS use were self-reported on a post travel survey within 8 weeks after return to the US.
- Elements captured in the survey included information regarding dietary habits during travel, diarrheal episodes, associated symptoms, perceived severity and incapacitation, and use of self-treatment.

## TD definition

- TD was defined as 3 or more loose stools within a 24 hour period, or 2 loose stools plus an associated symptom such as nausea, vomiting, abdominal pain, fever, blood in stool

## Statistical Analysis

A multivariate Poisson regression analysis was performed to examine the effects of the variables on TD risk

## Conclusions

- AS was not associated with TD, RR 1.18 (95% CI 0.97-1.44)
- Though not statistically significant, there was a trend towards significance for higher severity of the TD when patients were on AS, RR 1.16 (95% CI 0.82-1.62) in univariate analysis
- In a univariate analysis, AS was associated with TD if you are under age 50 RR 1.84 (95% CI CI: 1.42-2.34)
- This association was not observed in those above 50 years
- The higher frequency of achlorhydria in travelers over 50 year of age may have masked the association between AS and TD
- These findings supported previously identified risk factors for TD

## Acknowledgments

**Disclaimer:** The view(s) expressed herein are those of the authors and do not reflect the official policy or position of the Walter Reed National Military Medical Center, the San Antonio Military Medical Center, the Infectious Disease Clinical Research Program, the Uniformed Services University of the Health Sciences, the Naval Infectious Disease Diagnostic Laboratory, the Madigan Army Medical Center, the Naval Health Research Center, the Naval Medical Center Portsmouth, the US Army Medical Department, the US Air Force Office of the Surgeon General, the US Army Office of the Surgeon General, the US Navy Office of the Surgeon General, the Department of the Air Force, the Department of the Army, the Department of the Navy, the Department of Defense, or the US Government.

**Funding:** This project was funded through the Infectious Disease Clinical Research Program of the Uniformed Services University of the Health Sciences.

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