Evaluation of NSAID Exposure as a Risk Factor for *Clostridium difficile* Infection (CDI): A Propensity-Score- Matched Case-Control Study

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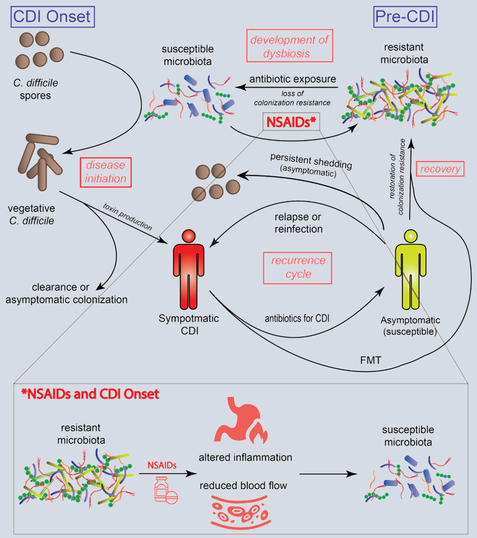
Background

- Prior studies have suggested an increased risk for **CDI** from exposure to certain Non-Steroidal Anti-Inflammatory Drugs (**NSAIDs**)



- Previous studies have been limited in the inclusion of over-the-counter medications – A major way patients acquire NSAIDs

Objective

Evaluate if the use of non-aspirin non-steroidal anti-inflammatory drugs increases the risk for development of *Clostridium difficile* infection.

Methods

Identification of Cases and Controls

- Subjects were selected from a previously identified cohort of patients who were tested for CDI in 2016
- Cases -> Positive for CDI; Controls -> Negative for CDI

Data Collection

- EMERSE[1] used to electronically query notes to identify non-aspirin NSAID use
- Any use within 30 days (including PRN) considered positive
- Comorbidity & baseline laboratory data abstracted electronically
- Random forest model was used to impute missing comorbidity and baseline data

Creation of Propensity Score

- Logistic regression model
- Variables Included: Gender, back pain, baseline serum creatinine, osteoarthritis, rheumatoid arthritis, serum albumin, and use of anticoagulant or antiplatelet medications

Matching

- Cases matched 1:1 with controls by propensity score
- Matching caliper was 0.2 x standard deviation of the logit of the propensity score

Analysis

- Conditional logistic regression used to compare cases to controls

Conclusion

NSAID use is not associated with an increased risk of *Clostridium difficile* infection

Results

Table: Study Population and Modeling Results

			Multivariable Model	
Variable, n (%) or mean ±SD	**Cases (N=628)**	**Controls (N=628)**	**OR [95% CI]**	**P**
Non-aspirin NSAID[a]	**140 (22.3)**	**161 (25.6)**	**0.97 [0.72,1.29]**	**.816**
Age	58.0 ± 18.2	56.2 ± 17.4	1.09 [1.01, 1.17][b]	.02
Weighted Elixhauser score**	11.6 ± 10.8	13.99 ± 11.8	0.98 [0.97,0.99]	<.001
Prior CDI**	185 (29.5)	82 (13.1)	2.64 [1.96, 3.56]	<.001
White race	542 (86.3)	522 (83.1)		
BMI*	27.4 ± 6.8	28.4 ± 8.6		
Proton pump inhibitor use**	234 (37.3)	282 (44.9)		
Baseline hemoglobin (g/dl)*	10.3 ± 2.3	10.0 ± 2.4		
Serum 25-OH vitamin D (ng/ml)	25.9 ± 6.9	25.1 ± 6.5		
Inflammatory bowel disease	108 (17.2)	96 (15.3)		
# Hospitalizations in year prior to CDI	0.13 ± 0.4	0.16 ± 0.4		
# Positive prior CDI episodes**	0.6 ± 1.3	0.3 ±1.0		

* p on unadjusted model < .05; ** p on unadjusted model < .01; [a]In prior 30 days; [b]per 10-year increase
Abbreviations: BMI, body mass index; CDI, *C. difficile* infection; NSAID, non-steroidal anti-inflammatory drug

Results

Figure 1: No Difference in NSAID Use Between Cases and Controls

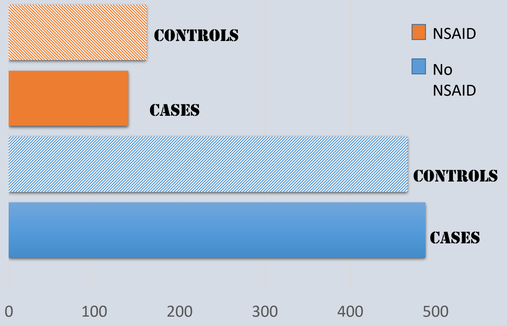


Figure 2: Patients With Prior History of CDI Have Increased Risk of CDI Regardless of NSAID Use

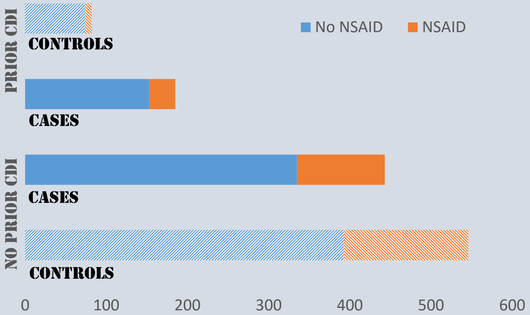


Figure 3: Despite Modeling Results – Significant Overlap In Burden of Comorbid Disease

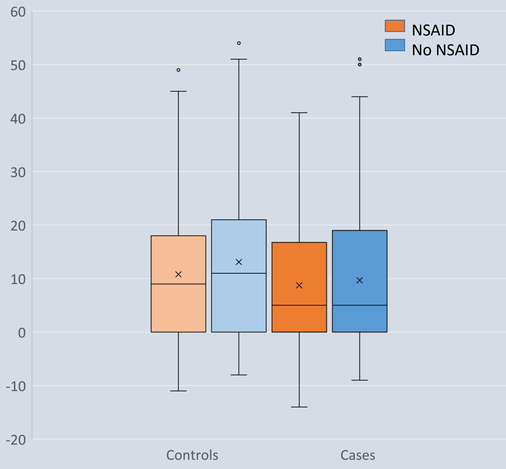
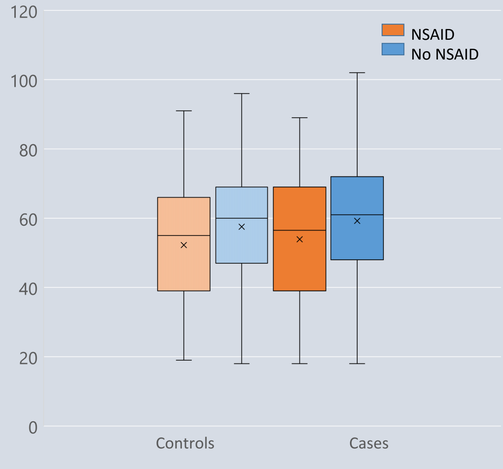


Figure 4: Despite Modeling Results - Significant Overlap in Age



Future Directions

An RCT run by investigators at Vanderbilt will evaluate the role of NSAIDs in CDI severity and the potential therapeutic role of misoprostol

1. Acknowledgement: Hanauer DA, Mei Q, Law J, Khanna R, Zheng K. Supporting information retrieval from electronic health records: A report of University of Michigan's nine-year experience in developing and using the Electronic Medical Record Search Engine (EMERSE). J Biomed Inform. 2015 Jun;55:290-300. doi: 10.1016/j.jbi.2015.05.003. Epub 2015 May 13. PMID: 25979153; PMCID: PMC4527540.