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Association of Acid Suppression Therapy with *Clostridium difficile* Infection in Hospitalized Patients on Antibiotics

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Abstract

Objective: The purpose of this study was to evaluate the risk of using acid suppression therapy (AST) in causing hospital-acquired *Clostridium difficile* infection (CDI) in hospitalized patients receiving antibiotics.

Methods: The study was a retrospective cohort analysis in a single-center from January 1, 2016 to December 31, 2017. A total of 4,833 patients were included. The incidence of CDI was analyzed in patients on antimicrobial therapy who were prescribed histamine-2 blockers (H_2 blockers), proton pump inhibitors (PPIs), both H_2 blockers and PPIs, or no AST

Results: The effect of AST was evaluated in groups of patients that received both high and low-risk antibiotics. Patients receiving only H_2 blockers for AST had a higher incidence of CDI [1.5% vs 0.9%] compared with those without AST, but this did not reach significance (p = 0.4440). Patients receiving only PPIs for acid suppression, and PPIs plus H_2 blockers together had a statistically significant increase in CDI incidence (p = 0.0046 and 0.0023, respectively).

Conclusion: PPIs are associated with a significantly increased risk of developing CDI for patients on antibiotics. Patients treated with H_2 blockers alone have a higher, but not statistically significant, rate of CDI when compared with those who did not receive them.

Keywords: CDI; *C. difficile* infection; antibiotics; PPIs; H_2 blocker

Introduction

Clostridium difficile is a spore-forming, gram-positive bacillus, and is a common cause of nosocomial infection. Complications of *C. difficile* infection (CDI) can lead to colitis, colectomy, and death [1,2]. Most infections are nosocomial, making prevention an important part of patient care [3]. Established risk factors for CDI among hospitalized patients include increased age, impaired renal function, use of immunosuppressant drugs, severe underlying illness, nonsurgical gastrointestinal procedures, and low serum albumin [4,5,6]. Antibiotics are the most widely implicated modifiable risk factor for CDI [7].

This is believed to be due to the disruption of normal intestinal flora, resulting in *C. difficile* overgrowth [8]. Although antibiotics have been divided into high-risk and low-risk categories in causing CDI [9], some studies implicate all antibiotics to be associated with the infection [2]. Recently, acid suppression therapy (AST) in the form of proton pump inhibitors (PPIs) and/or hitamine-2 receptor blockers (H_2 blockers) has also been posited as a risk factor. This claim is based on the finding that more acidic gastric contents kill *C. difficile* more effectively than less acidic contents, and AST is known to decrease acidity [10]. We performed a retrospective cohort study to investigate the effects of AST in causing CDI in patients already receiving antimicrobial therapy.

Objective

The purpose of the study was to identify the risk of hospital-acquired CDI while patients are on AST. It examined

the association of H_2 blockers and/or PPIs with the risk of developing CDI.

Methods

Setting and Study Period

This study is a retrospective cohort analysis including all adult patients who received antibiotics at UnityPoint Health-St. Luke's, Sioux City, Iowa between January 1st, 2016 and December 31st, 2017. The study was approved by the local Institutional Review Board.

Patient Selection

Patients were included if they were 18 years or older, had received at least one dose of an antibiotic during admission, were admitted during the study period, and had a length of stay greater than 3 days. Patients were excluded if they had a previous positive *C. difficile* result within 90 days of admission and if they had a previous inpatient stay within 4 weeks of the *C. difficile* positive result.

Case-Control Study

Patients with hospital-acquired CDI were defined as cases if they had a positive *C. difficile* result on or after the 4th day of admission, with no previous positive result within 90 days of admission, and no previous inpatient stay within 4 weeks of the relevant positive *C. difficile* result. Control subjects were chosen if they had received any antibiotics without AST while in the hospital during the study period. To ensure adequate exposure time, patients were included if they were admitted for greater than 3 days. To be considered exposed to AST, a patient must have received at least one dose of a PPI, an H_2 blocker, or both during admission. Patients were further grouped based on the type of antibiotic they received, high-risk antibiotics, low-risk antibiotics, or both. High-risk antibiotics were defined as fluoroquinolones, cephalosporins, intravenous β–lactam/β-lactamase inhibitor combinations, macrolides, clindamycin, and carbapenems. All other types of antibiotics were considered low-risk [9,11].

Data Analysis

The incidence of CDI was determined in the groups who received no AST, and those who received PPIs and H_2 blockers, separately and in various combinations. A two-tailed Fisher exact test compared the various cohorts and control groups (Table 1,2 and 4). A two-tailed Student t-test was employed to compare age and length of stay between the general sample population and CDI patients (Table 3).

Table 1: Data analysis: Acid Suppression Therapy (AST). In the combined AST group, the rate of CDI = 41/1,604 (2.6%); p = 0.0017. P values < 0.05 are considered significant.

Therapy Group	Total (*n*)	CDI cases (n, %)	p^2
High Risk + Low Risk antibiotics + No AST (Control Group)	1,170	11 (0.9)	--
High Risk + Low Risk antibiotics + H_2 blockers only	200	3 (1.5)	0.4440
High Risk + Low Risk Antibiotics + PPIs only	1,254	31 (2.4)	0.0046
High Risk + Low Risk Antibiotics + PPIs and H_2 blockers	150	7 (4.6)	0.0023

Table 2: Data Analysis: Patients on High-risk vs Low-risk antibiotics. *P values < 0.05 are considered significant.

Therapy Group	Total (*n*)	CDI cases (*n*, %)	*p**
High Risk antibiotics (without AST)	913	4 (0.4)	0.459
Low Risk antibiotics (without AST)	100	1 (1)	
High Risk antibiotics + PPIs only	719	2 (0.3)	0.011
Low Risk antibiotics + PPIs only	89	3 (3.3)	
High Risk antibiotics + PPIs or H_2 blockers	933	2 (0.2)	0.010
Low Risk antibiotics + PPIs or H_2 blockers	113	3 (2.7)	

Table 3: Baseline characteristics. *P values < 0.05 are considered significant.

Demographic characteristics	Entire population (*n* = 4,833)	Hospital-acquired CDI patients (*n* = 62)	*p**
Age (years)	Mean (SD): 61.8 ± 19.8	64.8 ± 16.7	0.2351
	Median: 64	66	
Gender (%)	Female: 59.9	59.7	
	Male: 40.1	40.3	
Length of Stay (days)	Mean (SD): 7.5 ± 5.5	12.5 ± 9.6	<0.0001
	Median: 6	9	

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Results

After exclusion, 4,833 patients were selected for analysis. Patients treated with PPIs, H_2 blockers and the corresponding CDI were categorized into groups (Table 4). The average age of the entire population was approximately 62, while the case population was approximately 65. The female to male ratio did not differ between the cases and the rest of the population. The length of stay was significantly greater for the CDI patients (12.5 days vs. 7.5 days), which is in general agreement with previously reported increased length of stay by 3-5 days [2].

Table 4: Study population (*n* = 4,833) on antibiotics. **P* values < 0.05 are considered significant.

AST	Patients receiving AST (*n*)	CDI Diagnosed (*n*)	% of CDI diagnosed	*p* value*
No AST (Control Group)	2,183	16	0.73	Referent
PPIs	2,062	36	1.75	0.0031
H2 blockers	372	3	0.81	0.7497
PPIs and H2 blockers	216	7	3.24	0.0030

More than half of the patients in the study received at least one dose of both high and low-risk antibiotics (n = 2,774), so incidence of CDI was compared among patients who had received both types of antibiotics (Table 4). Patients who had received high and low-risk antibiotics with no AST were used as a control group. Groups containing patients treated with PPIs only, and PPIs and H_2 blockers together, had a statistically higher incidence of CDI (p = 0.0046 and 0.0023, respectively). Patients receiving H_2 blockers had a higher incidence of CDI than those who did not receive them (1.5% vs. 0.9%), but this did not reach statistical significance (p = 0.4440). Unexpectedly, patients on low-risk antibiotics who received AST had a significantly higher incidence of CDI than the corresponding group on high risk antibiotics (Table 1).

Discussion

This study found that there was a statistically significant association between PPIs and CDI in patients who were prescribed antimicrobials. Faleck et al. [12] reported that in patients who did not receive antibiotics, PPIs alone were not a significant risk factor for CDI. Our study showed PPIs are a significant risk factor for CDI when they are used along with antimicrobials. This was found to be true in therapy groups involving both PPIs alone, and PPIs in combination with H_2 blockers. The higher rate of CDI cases in the AST group (2.6%) compared to those who did not receive AST (0.9%) (Table 1) was in alignment with similar trends observed by Howell et al. [9] A systematic review and meta-analysis by Tleyjeh et al. [13] demonstrated a strong association between H_2 blockers and CDI in hospitalized patients who received antibiotics. In our study, a few patients received H_2 blockers as a sole AST.

The small sample size coupled with a low overall incidence of hospital-acquired CDI may have led to insufficient data points to fully assess the risk of H_2 blockers. This study also found unexpectedly that in some therapy groups, low-risk antibiotics had a significantly higher incidence of CDI than high-risk antibiotics. Because most patients included in the study had received at least one dose of high-risk and low-risk antibiotics, the sample sizes in these comparison groups were small. Nonetheless, the results of this analysis warrant further investigation.

Limitations

This study investigated only patients receiving AST during inpatient stay. This does not detect or differentiate long-term AST use from short-term AST use, which could potentially affect the risk of CDI. Similarly, patients on antibiotics prior to hospitalization were not identified. These patients may have had a higher CDI risk and could have affected results if these patients were not distributed evenly between therapy groups. Other causes of CDI have not totally been ruled out in the study population.

Conclusion

When combined with antimicrobial agents, PPIs pose a significantly increased risk of CDI. Although not significant, H_2 blockers can also be a risk factor.

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