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Guideline implementation is effective at reducing proton pump inhibitor use in hematology-oncology units: a multidisciplinary intervention for reducing *Clostridioides difficile* risk

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Abstract

We implemented a guideline for appropriate acid suppressant use in hematology-oncology patients. This intervention resulted in a sustained reduction in proton pump inhibitor (PPI) use without an increase in rates of gastrointestinal bleeding. Practice guidelines are effective in reducing PPI use, which is associated with risk of *Clostridioides difficile* infection.

INTRODUCTION

Clostridioides difficile is a common cause of healthcare-associated infections in patients with hematologic malignancy[1]. Proton-pump inhibitor (PPI) use has been associated with a significantly increased risk of *C. difficile* infection (CDI)[2,3]. At our institution, 40% of hematology-oncology patients with a positive *C. difficile* test received a PPI in the prior 72 hours[4]. We implemented a guideline for appropriate PPI use in our hematology-oncology

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units and evaluated its impact on rates of PPI administration and gastrointestinal (GI) bleeding.

METHODS

This study was conducted on three inpatient hematology-oncology units at the Hospital of the University of Pennsylvania, a 791-bed tertiary care medical center. The study guideline (Figure 1) was implemented on November 13, 2017 (See Supplementary Methods). We analyzed the impact of this intervention, comparing a 14-month baseline cohort (September 2016–October 2017) prior to implementation of the guideline to the 10-month intervention cohort (November 2017–August 2018) after implementation.

Our primary outcome of interest was rate of PPI use measured in days of therapy (DOT). We also ascertained rates of histamine-2 receptor antagonist (H2RA) administration and *C. difficile* positive tests[4]. Medical record review was performed in a subset of patients with medication orders for PPIs, comparing a 3-month period before (August 12, 2017 to November 12, 2017) and after the intervention (November 13, 2017 to February 13, 2018). Data that were collected included PPI indication (determined by review of clinical documentation), acid suppressant prescription prior to admission, symptomatic or endoscopic evidence of GI bleeding, and PPI continuation on discharge. This study was approved by the University of Pennsylvania Institutional Review Board. Statistical methods are described in the Supplementary Methods.

RESULTS

Compared to the baseline time period, there was a significant reduction in PPI use on the study units during the intervention period, from a mean of 1092.8 DOT/month (SD 113.5) to a mean of 752.4 DOT/month (SD 73.2) ($P<0.001$). This decline in PPI administration was sustained over the intervention period, with 661 DOT in the last month of the intervention, which represented a 48% decline from the peak of use in October 2016 (1275 DOT). Using segmented regression analysis, there was a significant immediate reduction with the intervention of 195.5 DOT (95% confidence interval [CI], reduction of 87.8 – 303.2; $P=0.001$) (Figure 2). Additionally, there was a significant post-intervention linear trend of a reduction in PPI administration of 18.2 DOT per month (95% CI reduction of 11.2 – 25.1; $P<0.001$). Assessing rate of PPI administration per 1000 patient days, model fit, change in y-intercept, and the post-intervention linear trend remained significant (Supplementary Table 1).

H2RA use increased from an average of 615.1 DOT (SD 124.1) in the baseline group compared to 714.1 DOT (SD 88.8) in the intervention group ($P=0.04$). Using segmented regression analysis, there was no immediate change after guideline introduction (reduction of 102.9 DOT (95% CI reduction of 247.6 – increase of 41.7); $P=0.15$). However, we found a significant post-intervention linear trend of an increase in H2RA use of 19.1 DOT per month (95% CI increase of 5.1 – 33.0; $P=0.01$). Assessing rate of H2RA administration per 1000 patient days, there was no significant change in either the immediate post-intervention change or linear trend.

In medical record review of a subset of patients, there were 155 PPI medication orders in the baseline cohort and 126 in the intervention cohort (Supplementary Table 2). Of these, the majority represented continuation of a prior-to-admission medication; only 43 (28%) in the baseline and 23 (18%) in the intervention group were new orders (P=0.047). There was no difference in the order indication across time periods. An increased proportion of PPIs were continued on discharge in the intervention group compared to the baseline group (85% vs 70%, P=0.004). The majority of these represented continuation of a prior-to-admission medication (94/106 in the baseline group and 95/107 in the intervention group).

Rates of GI bleeding in this subset of patients were low, 6 (3.9%) in the baseline group compared to 6 (4.8%) in the intervention group (P=0.75). There were no significant differences in other secondary outcomes between the groups (Supplementary Table 3).

There was no significant change in rates of *C.difficile* positive tests on study units, with an average of 2.057/1000 patient days (SD 1.289) in the baseline group and 2.046/1000 patient days (SD 0.959) in the intervention group (P=0.93). However, the study was not powered to determine an impact of our intervention on rates of *C.difficile*.

DISCUSSION

We evaluated the impact of implementation of a multidisciplinary guideline for appropriate acid suppression in our hematology-oncology population. Our results were notable for several findings. First, we demonstrated a large and sustained decline in PPI administration with guideline implementation. Second, while not statistically significant, there was a trend towards decreased inappropriate ordering for GI bleeding prophylaxis during chemotherapy. Finally, there was no increase in rates of GI bleeding, indicating low risk of harm with our intervention.

In a population with high rates of colonization and infection with *C. difficile*,[1–3] it is important to reduce unnecessary exposures that increase the risk of CDI. Implementation of our guideline resulted in an average 31% reduction in PPI use over time, with a sustained decline over the study period. Prior studies have investigated various methods of reducing PPI utilization in general medical patients, including a pharmacist-led inpatient PPI stewardship team[5] and computerized order entry alerts with prospective audit and feedback[6]. These interventions have demonstrated similar levels of success with approximately 41% and 37% reductions, respectively. Our study focused on patients with hematologic malignancy and addressed acid suppressant guidelines unique to this population, prophylactic acid suppressant use, and symptomatic management during chemotherapy. We believe that addressing these areas of frequent, often inappropriate, utilization of acid suppressants in this patient population contributed to the success of our intervention without the need for prospective audit and feedback.

While we noted a decrease in rates of PPI use, our intervention may have resulted in increased utilization of H2RAs. However, after adjusting for patient days on study units, there was no significant increase in H2RA use. Additionally, while H2RA agents have also

been associated with risk of CDI, they carry a 29% lower odds of CDI when compared to PPIs[7,8].

There was no increased rate of GI bleeding with our intervention. This is consistent with previous studies that have shown that serious adverse events such as requirement for blood transfusion is uncommon after chemotherapy[9]. Additionally, rates of GI bleeding with systemic corticosteroid use has been found to be similar to placebo in meta-analysis[10].

Our study has potential limitations. First, we utilized a quasi-experimental design, which may be biased by confounding variables that impacted PPI prescribing. However, there were no additional interventions focused on PPI prescribing during the study period. Second, this study was one of multiple ongoing interventions targeted towards reducing *C. difficile* rates, and was not powered to detect a significant change in this outcome. Additionally, our study focused on hematology-oncology patients at an academic institution and may not be generalizable to dissimilar populations. Finally, high rates of orders with unclear indications and continuation on discharge in the intervention group suggests opportunity for additional improvement.

In conclusion, our findings highlight the impact of a multidisciplinary practice guideline in effectively reducing PPI use in hospitalized patients with hematologic malignancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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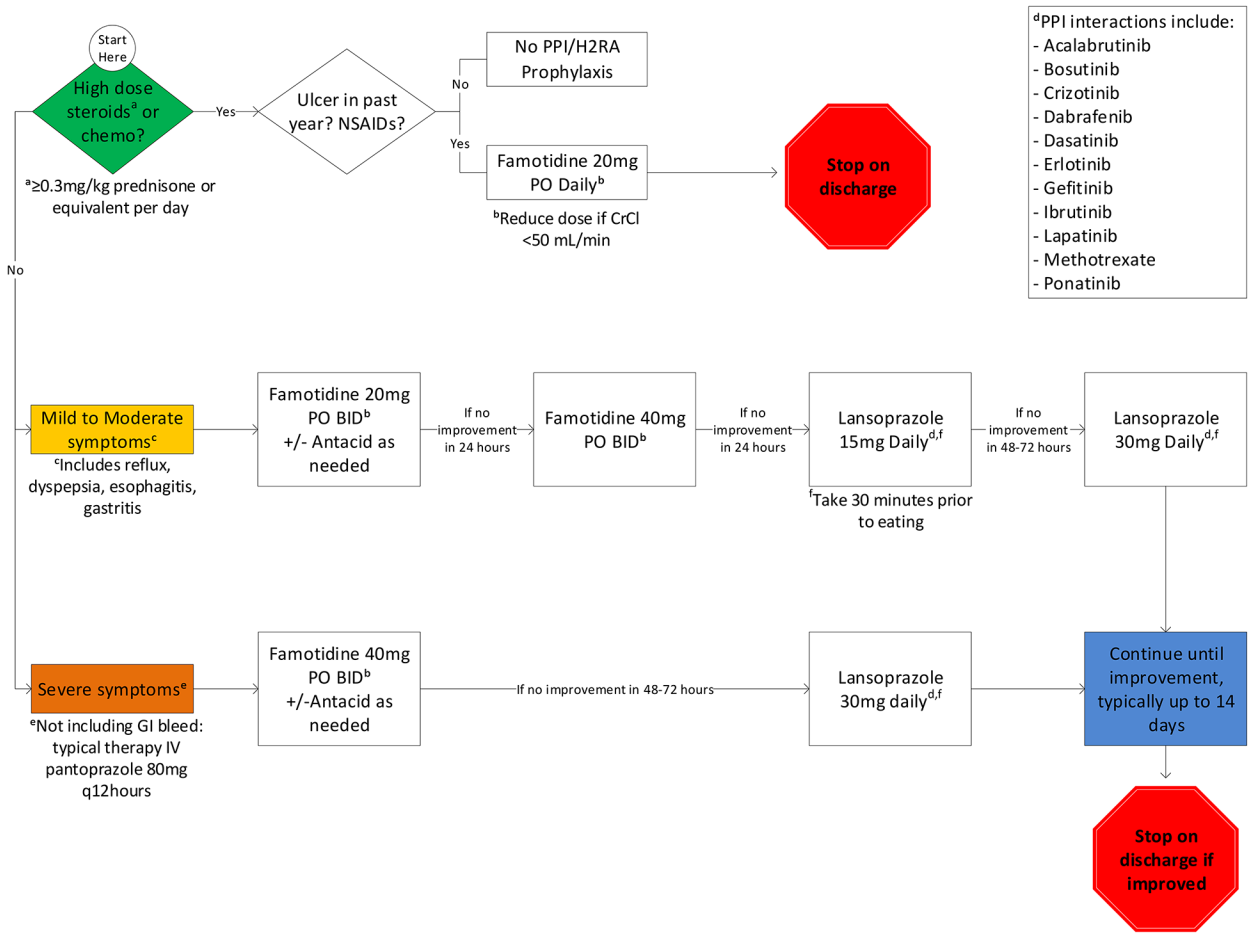

Figure 1.

Guideline for acid suppression in hematology-oncology patients NOTE. Chemo, chemotherapy; NSAIDs, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitor; H2RA, histamine-2 receptor antagonist; CrCl, creatinine clearance; GI, gastrointestinal

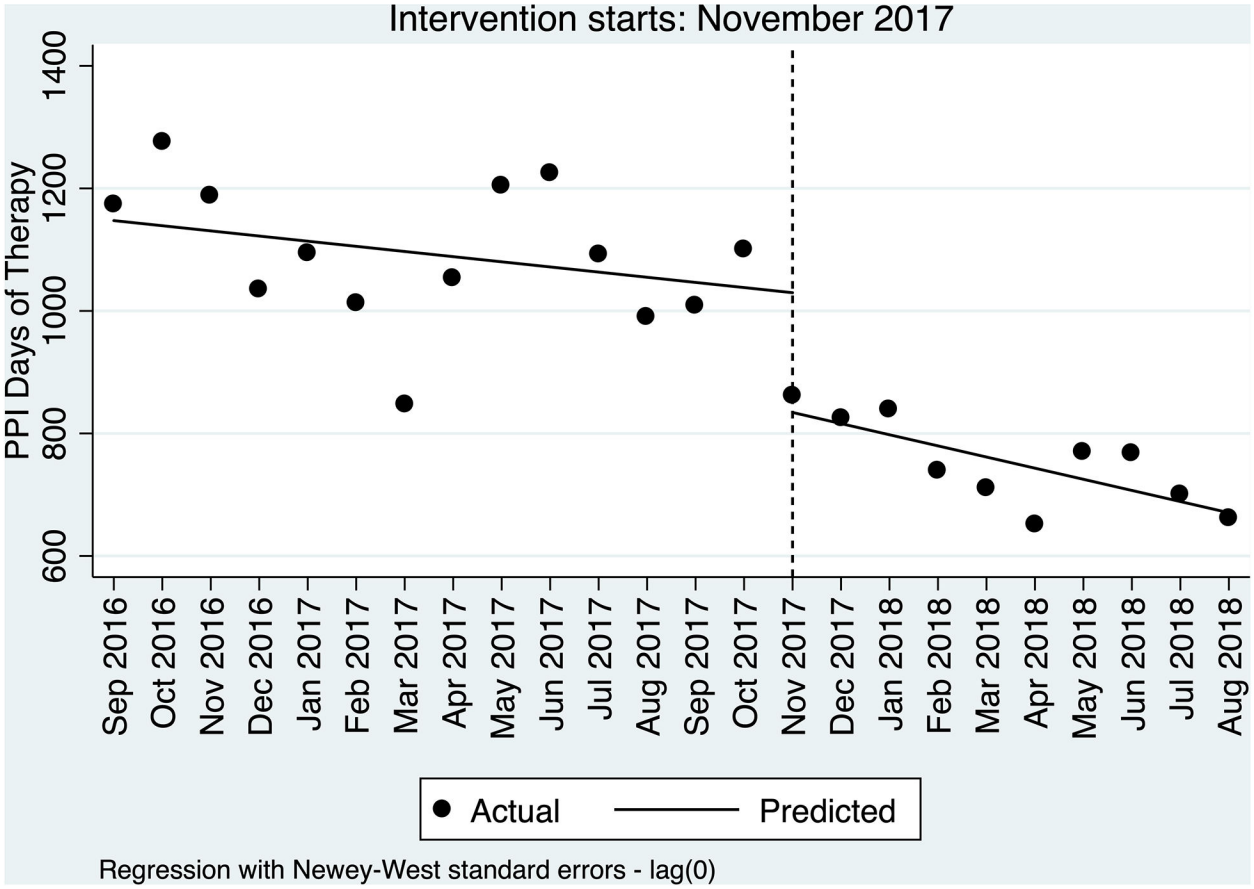

Figure 2.

Segmented regression analysis of monthly proton pump inhibitor administration on three hematology-oncology units NOTE. PPI, proton pump inhibitor