ORIGINAL RESEARCH

Defining Appropriate Use of Proton-Pump Inhibitors Among Medical Inpatients

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BACKGROUND: Proton-pump inhibitors (PPIs) are commonly used among medical inpatients, both for prophylaxis against upper gastrointestinal bleeding (UGIB) and continuation of outpatient use. While PPIs reduce the risk of UGIB, they also appear to increase the risk of hospital-acquired pneumonia (HAP) and *Clostridium difficile* infection (CDI). Depending upon the underlying risks of these conditions and the changes in those risks with PPIs, use of proton-pump inhibitors may lead to a net benefit or net harm among medical inpatients.

OBJECTIVE: We aimed to determine the net impact of PPIs on hospital mortality among medical inpatients.

DESIGN: A microsimulation model, using literature-derived estimates of the risks of UGIB, HAP, and CDI among medical inpatients, along with the changes in risk associated with PPI use for each of these outcomes. The primary outcome was change in inpatient mortality.

PARTICIPANTS: Simulated general medical inpatients outside the intensive care unit (ICU).

MAIN MEASURE: Change in overall mortality during hospitalization.

KEY RESULTS: New initiation of PPI therapy led to an increase in hospital mortality in about 90 % of simulated patients. Continuation of outpatient PPI therapy on admission led to net increase in hospital mortality in 79 % of simulated patients. Results were robust to both one-way and multivariate sensitivity analyses, with net harm occurring in at least two-thirds of patients in all scenarios.

CONCLUSIONS: For the majority of medical inpatients outside the ICU, use of PPIs likely leads to a net increase in hospital mortality. Even in patients at particularly high risk of UGIB, only those at the very lowest risk of HCAP and CDI should be considered for prophylactic PPI use. Continuation of outpatient PPIs may also increase expected hospital mortality. Apart from patients with active UGIB, use of PPIs in hospitalized patients should be discouraged.

KEY WORDS: simulation; modeling; hospital medicine; medical decision making.

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INTRODUCTION

Proton-pump inhibitors (PPIs) are commonly used among medical inpatients. An estimated 50 % of inpatients are prescribed PPIs, including between 15 and 25 % who are prescribed these agents specifically for prophylaxis of upper gastrointestinal bleeding (UGIB).^{1–4} However, only two small controlled trials of prophylaxis exist in the inpatient population outside of the intensive care unit (ICU).⁴ Thus, evidence to support this practice is largely extrapolated from studies carried out within ICUs, where risk of UGIB is substantially greater due to the frequent presence of respiratory failure.⁵ Nevertheless, it is reasonable to conclude that PPIs do reduce the risk of clinically significant UGIB among non-ICU inpatients.

Unfortunately, enthusiasm for routine use of PPIs is tempered by evidence that PPIs are associated with increased risk of hospital-acquired pneumonia (HAP) and *Clostridium difficile* infection (CDI).^{1,6,7} Because these conditions are common and often have worse outcomes than UGIB, many authors have suggested that prophylactic PPI use should be avoided in most hospitalized patients.^{2,3,7,8} Overuse is sufficiently common that, as one of its recommendations for the American Board of Internal Medicine (ABIM) Foundation's *Choosing Wisely* campaign, the Society of Hospital Medicine recommended against stress ulcer prophylaxis “unless at high risk for GI complications”.⁹ However, there are no published analyses examining how the tradeoffs between UGIB risk and HAP and CDI risk affect the net effect of acid suppression on inpatient mortality, nor are there studies examining how variation in patient risk of UGIB, HAP, and CDI should affect individual decisions about use of PPIs. The different underlying risks of UGIB, HAP, and CDI, along with the different relative risks for each of these conditions with PPI use, may lead to subpopulations of inpatients in whom PPI use may either increase or decrease overall mortality. Using modeling and simulation techniques and literature-derived distributions of the risk and case fatality of the major conditions affected by PPI use, we sought to examine the overall impact of the two most common indications for inpatient PPI use—inpatient

stress ulcer prophylaxis and continuation of outpatient use—on inpatient mortality. In addition, we sought to better define populations of inpatients outside the ICU for whom each type of use might yield a net benefit or harm.

METHODS

We created a microsimulation model to examine the effect of PPI continuation or initiation on in-hospital mortality among medical inpatients outside the ICU. To estimate the impact of PPI use, we modeled the risk of each of the three outcomes of interest (UGIB, HAP, and CDI), and in our base case analysis, assumed a causal linkage between PPI use and the risk of each of these outcomes.

A causal link between PPI use and reduction in UGIB risk is well-supported both in theory and published data from ICU studies,^{5,10–12} although there are limited randomized controlled trial data outside that setting.⁴ The causal linkages between acid suppressive therapy and each of HAP and CDI are perhaps less well established. For each of these conditions, observational studies have shown clear and consistent associations with acid suppressive therapy, and there appear to be dose-response relationships and clear temporal relationships between initiation of therapy and risk of both HAP and CDI.^{6,7,13–18} Additionally, separate work in healthy volunteers has delineated a plausible biologic mechanism by which acid suppression would increase the risk of pneumonia.^{19,20} To our knowledge, investigations into the mechanism through which PPIs increase risk of CDI have been limited to animal models and culture data, and some conflict remains.^{21–23} Thus, while not definitively proven in clinical trials, a preponderance of observational evidence appears to support a causal linkage between acid suppression and risk of both HAP and CDI, with the mechanistic linkage between PPIs and CDI somewhat less certain.

SOURCES OF MODEL PROBABILITIES

We first sought to identify the best available literature estimates and distribution of the incidence of UGIB, HAP, and CDI, the case fatality associated with UGIB, HAP, and CDI, and the odds ratios conferred upon UGIB, HAP, and CDI by initiation or continuation of PPI therapy. To do so, we conducted a literature search using the MEDLINE database, and used data from the Healthcare Cost and Utilization Project's National Inpatient Sample (HCUP NIS) to verify and supplement rates found in the literature;²⁴ further detail regarding our literature search strategy can be found in the [Online appendix](#).

The risks of UGIB, HAP, and CDI varied widely in the identified literature. Estimates of nosocomial UGIB risk in non-ICU patients range from 0.22 % to 0.4 %, depending upon the cohort and definition of UGIB used (e.g., endoscopically proven vs. hematemesis or melena vs. occult bleeding with drop in hemoglobin).^{1,25} Estimates of the incidence of

HAP outside the ICU range between 0.3 % and 4.9 %, again varying by cohort and case definition.^{6,26,27} Point estimates of the risk of hospital-acquired CDI in academic medical centers range from 0.7 % to 2.25 % (during an outbreak).^{7,28–31} Surveillance data from Canada (where CDI is a reportable infection) suggest an overall rate of 0.46 %, with 95 % confidence intervals from 0.34 % to 0.84 %.³² Some portion of this risk is attributable to use of acid suppressive medications, though CDI incidence among patients not taking either PPIs or histamine2-receptor antagonists is infrequently reported. Howell and colleagues report the CDI incidence at their center among patients not prescribed any form of acid suppressive therapy to be 0.3 %.⁷ Many authors reported incidence rates rather than overall incidence; these ranged from 6.5 to 28.1 cases per 10,000 patient-days, with an overall trend that appears to be increasing over time.^{29,33,34}

Outcomes of UGIB, HAP, and CDI among inpatients were similarly varied in our literature search. For example, in data validating the Rockall score for risk prediction in UGIB, mortality ranged from 0 % to 46.5 %, depending on various risk characteristics.^{35,36} HAP was associated with in-hospital mortality of 18.4 % in an Italian cohort, 18.8 % mortality in a United States cohort, and 26 % (with 14 % mortality attributed to pneumonia) in a study of patients in Spain.^{15,26,37} Hospital-acquired CDI was associated with an 11 % absolute increase in hospital mortality in one study; another found that attributable mortality varied with age from 0 to 14.0 %.^{38,39} Dubberke and colleagues reported attributable mortality after 180 days to be 5.7 %.⁴⁰

The impact of acid suppression therapy on each of the considered conditions varied as well. Herzig and colleagues found adjusted odds ratios with PPI use of 0.58 and 1.3 for nosocomial GI bleed and HAP, respectively.^{1,6} Using the same data set, Howell and colleagues found odds ratios for CDI ranging from 1.53 to 2.36, with more intensive acid suppression associated with higher risk of CDI.⁷ Meanwhile, two meta-analyses found pooled odds ratios of CDI with PPI use of 1.74 and 1.69.^{41,42}

Studies of outpatient PPI use have demonstrated a possible diminishing risk of pneumonia with longer durations of acid suppressive therapy.^{14,43} Because similar data are not available for discontinuation of PPIs when chronic users are hospitalized, we assumed that the lowest odds ratio observed among outpatients would apply to discontinuation among inpatients. That is, we assumed that chronic users who continued to receive PPIs during hospitalization would be subject to an odds ratio of HAP of 1.09, compared to a mean OR of 1.28 with new PPI initiation.¹⁴

For each of our parameters, we used literature estimates that included information regarding variance (quartiles, deciles, confidence intervals, etc.), rather than point estimates, ensuring that our ranges for each parameter included other estimates identified in our literature search. The base case and distributions for each major assumption are shown in Table 1. We modeled most parameters as normal distributions, with mean

Table 1 Characteristics of Modeled Distributions of Key Variables After a Representative 200,000-Patient Sample

Modeled variable (fitted to literature value; origins detailed in text)	Mean	5th percentile	50th percentile	95th percentile	References
Incidence of UGIB	1.0 %	0.0 %	0.5 %	3.7 %	See Online appendix, ^{1,25,44}
Incidence of HAP	2.8 %	0.5 %	2.7 %	5.4 %	See Online appendix, ⁶
Incidence of CDI	0.5 %	0.3 %	0.5 %	0.8 %	See Online appendix, ^{7,24}
Case fatality of UGIB	12.3 %	0.0 %	8.8 %	43.4 %	35,36
Case fatality of HAP	18.5 %	6.8 %	18.4 %	30.4 %	15,26,37
Case fatality of CDI	6.5 %	1.0 %	6.2 %	12.9 %	31,32,39,40,46
Odds ratio for UGIB with acid suppression	0.59	0.43	0.58	0.78	1
Odds ratio for HAP with PPI initiation	1.28	1.13	1.28	1.43	6
Odds ratio for HAP with PPI continuation	1.09	1.03	1.09	1.16	14,43
Odds ratio for CDI with acid suppression	1.74	1.39	1.74	2.08	7,41,42

and standard deviation to yield a distribution matching that of reported confidence intervals. This was the case for the incidence of HAP, case fatality rates of HAP and CDI, and odds ratios of UGIB, HAP, and CDI.^{6,7,15} If more detailed information on distributions was available, we used the distribution that best fit the published estimates. For example, a Weibull distribution was created to match Herzig and colleagues' reported incidence of UGIB.⁴⁴ To estimate the case fatality rate of UGIB, a normal distribution was fitted to Vreeburg and colleagues' reported mean and standard deviation Rockall score.³⁶ This distribution was used to generate Rockall scores as a categorical variable, yielding an expected frequency of UGIBs of each severity. As described above, many definitions of UGIB are used in the literature; by adopting the data published by Rockall and colleagues, we also adopted their definition. The combined Rockall and Vreeburg validation set was used to estimate mortality within each subgroup.³⁶ Estimates of CDI incidence are complicated by increasing rates over time and wide variation among hospitals and regions. Because we were unable to identify recent, nationally representative estimates of CDI incidence with information regarding variance, we estimated this distribution from the NIS database. We used multiple methods, finding convergence between methods of estimation. Further detail regarding this incidence estimate can be found in the Online appendix. The mean, median, 5th, and 95th percentile of probability distributions for key variables from a representative simulation are included in Table 1.

We then performed a Monte Carlo simulation, estimating the change in hospital mortality from PPI initiation or continuation for hypothetical cohorts of patients sampled from the above-detailed probability distributions. Given the somewhat less robust mechanistic evidence linking acid suppressive therapy and CDI, we performed separate simulations with and without an effect of PPIs on CDI risk. Because our focus was on PPI use among inpatients, we limited our analysis to hospital mortality, and did not consider potential effects on other outcomes associated with longer-term use of PPI therapy, such as B-12 deficiency, hip fracture, or altered medication absorption.⁸

Version 13 of Stata was used to analyze the NIS dataset and obtain a distribution of CDI. All other analysis and simulation was performed in R (version 3.1).

RESULTS

The primary results of our simulation are shown in Figures 1 and 2. Assuming a causal link between PPI use and CDI, in approximately 90 % of simulated cases, initiation of PPIs for prophylaxis led to a net increase in expected mortality, and therefore likely represents harm to the overwhelming majority of hospitalized patients. When we simulated the alternate case where PPIs do not contribute to risk of CDI, new initiation of PPI therapy leads to expected net harm in approximately 86 % of hospitalized patients. A density plot, showing the distribution of impact on expected mortality under these two assumptions, is shown in Fig. 1. In our base-case analysis, the number-needed-to-harm (the number of patients who would be newly initiated on a PPI for prophylaxis to cause one additional inpatient death) is approximately 830.

Our simulation of PPI discontinuation among chronic users during hospitalization showed that continuation of PPIs would lead to increase in expected mortality in approximately 80 % of patients, and in 68 % of patients in the case where PPIs do not contribute to risk of CDI. A density plot showing the results of our simulation under these assumptions is shown in Fig. 2.

To better define the effects of prophylactic PPI use on specific risk groups within the inpatient population, we prepared tables examining the net effect on mortality of PPI use across the probabilities of each complication. The base case estimate (allowing the probability of HAP, case fatality of UGIB, case fatality of HAP, and case fatality of CDI all to be at the 50th percentile) is shown in Table 2A; at all deciles of CDI and UGIB risk, prophylactic PPI use would lead to net harm. A more favorable case for PPI prophylaxis emerges in Table 2B, wherein we have used the 10th percentile for probability of HAP, case fatality of HAP, and case fatality of CDI, and the 90th percentile of UGIB case fatality. In this case, which is strongly biased in favor of PPI use, approximately half of patients would benefit from PPI prophylaxis. Put another way, even in a scenario that is skewed to heavily favor the prophylactic use of PPIs, the net effect on inpatient mortality is zero.

In our base case scenario, only extreme outliers in underlying risks stand to benefit from PPI prophylaxis. Assuming a HAP risk at the median, even a patient in the highest decile of

Fig. 1 Density plot of change in expected mortality with newly-initiated PPI, assuming increased risk of CDI with acid suppression (*black*) and assuming no increased risk of CDI (*gray*). The mean impact of PPI initiation on expected mortality is indicated by *dashed vertical lines*. Patients to the left of zero receive a net benefit, while patients to the right of zero are harmed.

UGIB risk and lowest decile of CDI risk stands to be harmed (Table 2). At the lowest decile of HAP risk, only patients in the highest decile of UGIB risk stand to receive benefit (not shown). In contrast to these examples, the typical inpatient is likely to be harmed by prophylactic use of PPIs.

DISCUSSION

Our study suggests that for the vast majority of medical inpatients, routine use of PPI therapy for UGIB prophylaxis is harmful, leading to a net increase in expected mortality. These results were robust to a wide variety of parameters and risk distributions. This strongly suggests that prophylaxis with PPIs is unwarranted in most patients. Additionally, we found that continuation of outpatient PPI use during hospitalization may also contribute to increased mortality. This finding suggests that discontinuation or down-titration of PPIs during hospitalization should be considered in patients who chronically take PPIs but are not at extremely high risk of UGIB (e.g., the majority of patients who take PPIs for symptoms of reflux or as prophylaxis while taking NSAIDs, steroids, or other medications of concern).

Our findings raise concern, because overuse of PPIs is common among inpatients, and this highlights the need for active methods of ensuring appropriate use. Even after interventions designed to be specifically intended to reduce PPI prescriptions among hospitalized patients, PPI use appears to be common: after such an intervention, Yachimski and colleagues reported that 16 % of admitted patients not taking a PPI on admission were prescribed PPIs during their hospitalization.³ In our model, approximately 10 % of patients derive benefit from prophylactic PPI therapy, suggesting that inappropriate use of these medications as prophylaxis outstrips helpful use by at least 60 %, even under the most generous of assumptions and following interventions designed to reduce PPI use.

While PPIs are clearly overused, our analysis also suggests that a small, very high-risk segment of inpatients may be well-served by prophylactic acid suppression. As with the outliers discussed above and shown in Table 2, patients stand to benefit from prophylactic acid suppression if the risk of UGIB and mortality is high and the risk of CDI and HAP (and associated mortality) are low. Identifying such patients requires careful risk prediction, and commonly used heuristics (such as using

Fig. 2 Density plot of change in expected mortality with continuation of chronic PPI on admission, assuming increased risk of CDI with acid suppression (*black*) and assuming no increased risk of CDI (*gray*). The mean impact of PPI continuation on expected mortality is indicated by *dashed vertical lines*.

PPIs in those who are prescribed steroids or NSAIDs) do not capture the tradeoffs that must be evaluated to optimally target acid suppressive therapy. Our risk tables suggest that increased risk of UGIB alone is not adequate; instead, identifying patients who may benefit requires prospective risk prediction tools for risks and fatality rates of UGIB, HAP, and CDI. The existing risk models we identified have not been fully validated. Further, many published risk prediction tools require data and calculations that would be best addressed by automated calculation performed in electronic medical records/order entry systems, rather than by individual clinicians.³⁰

Finally, our analysis raises questions regarding continuation of outpatient acid suppressive therapies. In our simulation of this scenario, continuing use of acid suppressive therapy among those hospitalized would lead to a small increase in expected mortality in around 80 % of patients. Even under the assumptions that PPIs do not contribute to increased risk of CDI and that continuation of outpatient therapy leads to a lesser increase in risk of HAP compared with new initiation, continuation of

outpatient therapy appears to lead to a small increase in expected mortality in over two-thirds of patients. Unfortunately, withholding long-term PPIs during hospitalization may lead to an increase in dyspeptic symptoms.⁴⁵ This particular action may therefore require setting appropriate patient expectations, and tolerance of said dyspeptic symptoms; alternatively, patients with severe dyspepsia may be willing to accept small risks of adverse events in order to minimize their symptoms. Ultimately, as with most decisions involving tradeoffs between symptomatic benefit and potential adverse events, individualized decision-making is warranted. Alternatively, for patients with severe rebound symptoms, hospital admission may be an opportunity to down-titrate acid suppressive regimens (e.g., to lower doses, to potentially less-harmful histamine-2 antagonists, or to as-needed antacids).

Our study is not without limitations. First, this is a modeling study, and is therefore reliant on literature-derived estimates of the risks and mortality associated with the conditions considered. Second, our distributions are fitted to published estimates, and may not be

Table 2 Calculated Change in Expected Mortality with PPI Initiation, at Deciles of UGIB Risk (Columns) and CDI Risk (Rows)

A. Base case scenario

Pre-intervention probability of CDI	Pre-intervention probability of GI bleed								
	0.04%	0.10%	0.20%	0.32%	0.49%	0.72%	1.05%	1.57%	2.56%
0.38%	0.16%	0.16%	0.15%	0.15%	0.14%	0.13%	0.12%	0.09%	0.05%
0.43%	0.16%	0.16%	0.16%	0.15%	0.14%	0.13%	0.12%	0.09%	0.05%
0.48%	0.17%	0.16%	0.16%	0.15%	0.14%	0.13%	0.12%	0.10%	0.05%
0.51%	0.17%	0.16%	0.16%	0.15%	0.15%	0.14%	0.12%	0.10%	0.05%
0.54%	0.17%	0.17%	0.16%	0.16%	0.15%	0.14%	0.12%	0.10%	0.06%
0.58%	0.17%	0.17%	0.16%	0.16%	0.15%	0.14%	0.12%	0.10%	0.06%
0.61%	0.17%	0.17%	0.16%	0.16%	0.15%	0.14%	0.13%	0.10%	0.06%
0.65%	0.17%	0.17%	0.17%	0.16%	0.15%	0.14%	0.13%	0.10%	0.06%
0.71%	0.18%	0.17%	0.17%	0.16%	0.15%	0.14%	0.13%	0.11%	0.06%

B. Scenario favoring PPI use: low case fatality rate for HAP, CDI, high case fatality rate for UGIB

Pre-intervention probability of CDI	Pre-intervention probability of GI bleed								
	0.04%	0.10%	0.20%	0.32%	0.49%	0.72%	1.05%	1.57%	2.56%
0.38%	0.03%	0.02%	0.01%	-0.00%	-0.02%	-0.04%	-0.07%	-0.11%	-0.20%
0.43%	0.03%	0.02%	0.01%	0.00%	-0.02%	-0.04%	-0.07%	-0.11%	-0.20%
0.48%	0.03%	0.02%	0.01%	0.00%	-0.01%	-0.04%	-0.06%	-0.11%	-0.20%
0.51%	0.03%	0.02%	0.01%	0.00%	-0.01%	-0.04%	-0.06%	-0.11%	-0.20%
0.54%	0.03%	0.02%	0.01%	0.00%	-0.01%	-0.03%	-0.06%	-0.11%	-0.20%
0.58%	0.03%	0.02%	0.01%	0.00%	-0.01%	-0.03%	-0.06%	-0.11%	-0.20%
0.61%	0.03%	0.02%	0.01%	0.00%	-0.01%	-0.03%	-0.06%	-0.11%	-0.20%
0.65%	0.03%	0.02%	0.01%	0.00%	-0.01%	-0.03%	-0.06%	-0.11%	-0.20%
0.71%	0.03%	0.02%	0.01%	0.00%	-0.01%	-0.03%	-0.06%	-0.11%	-0.20%

All numbers in percents. Negative numbers (shaded cells) indicate a net benefit is conferred by starting a PPI.

Table A (top) shows the base case (that is, assuming the mean for all of: probability of HAP, case fatality of UGIB, case fatality of HAP, and case fatality of CDI). Due to the skew in the distribution of UGIB mortality, using the mean rather than the median for UGIB case fatality overestimates the benefit of PPIs compared with the median. Using the median here would more accurately predict change in mortality for an average patient, but because we are estimating more favorable scenarios for PPI use, we have used the mean.

Table B (bottom) shows the 10th percentile for risk and case fatality of HAP, 10th percentile for case fatality of CDI, and 90th percentile for case fatality of UGIB. This represents patients both high risk for UGIB of high mortality and equally low risk of HAP and mortality from HAP and CDI.

representative of the patient population at any particular institution. Our results should be viewed in that context, and interpreted through the lens of local risks of these conditions. And finally, as discussed above, prospective risk assessments for UGIB, HAP, and CDI are limited at present. Available predictive models of UGIB have been retrospectively validated in multiple cohorts, but have not been prospectively validated. CDI risk prediction models have not been prospectively validated, and often rely on difficult-to-measure factors such as exposure to

Clostridium difficile. To our knowledge, no models predictive of HAP risk have been validated.

Despite these limitations, we posit that the use of PPIs either for inpatient prophylaxis or continuation of outpatient use likely leads to a small increase in expected hospital mortality for the majority of medical inpatients. Targeted use of PPIs to the small proportion of patients who may benefit is theoretically possible, but requires the development and validation of accurate risk prediction tools for risks and mortality from UGIB,

HAP, and CDI. Given the current lack of such tools, our results suggest that, excepting those who are being actively treated for UGIB, PPI use among general medical inpatients should generally be discouraged, even in those who have been taking them chronically.

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Compliance with Ethical Standards:

Conflicts of interest: The authors declare that they do not have a conflict of interest.

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