ORIGINAL RESEARCH
Economic Evaluation

Cost-Effectiveness Analysis: Stress Ulcer Bleeding Prophylaxis with Proton Pump Inhibitors, H2 Receptor Antagonists

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ABSTRACT

Objectives: Proton pump inhibitors (PPIs) and H2-receptor antagonists (H2RAs) present varying pharmacological efficacy in preventing stress ulcer bleeding (SUB) in intensive care units. The literature also reports disparate rates of ventilator-assisted pneumonia (VAP) as side effects of these treatments. We compared the cost-effectiveness of these two prophylactic pharmacological options. Methods: We constructed a decision tree with a 60-day time horizon for patients at high risk for developing SUB, receiving either PPIs or H2RAs. For each treatment strategy, patients could be in one of three states of health: SUB, VAP, or no complication. Contemporary, clinically relevant probabilities were obtained from a broad literature search. Costs were estimated by using a representative US countrywide database. A third-party payer perspective was adopted. Cost-effectiveness and univariate and multivariate sensitivity analyses were performed. Results: Probabilities of SUB and VAP were 1.3% and 10.3% for PPIs versus 6.6% and 10.3% for H2RAs, respectively. Lengths of stay and per diem costs were 24 days and US $2764 for SUB, 42 days and US $3310 for VAP, and 14 days and US $2993 for patients without complications. Average costs per no complication were US $58,700 for PPIs and US $63,920 for H2RAs. The H2RA strategy was dominated by PPIs. Sensitivity analysis showed that these findings were sensitive to VAP rates but PPIs remain cost-effective. The acceptability curve shows the stability of the probabilistic results according to varying willingness-to-pay values. Conclusion: PPI prophylaxis is the most efficient prophylactic strategy in patients at high risk of developing SUB when compared with using H2RAs. Keywords: cost-effectiveness, H2RA, proton pump inhibitors, stress ulcer bleeding.

Introduction

Stress-related mucosal disease in the form of stress ulcer bleeding (SUB) remains an important clinical problem. Although it is a small proportion of patients who bleed [1,2], the clinical factors that predict a higher risk of rebleeding are increasingly found among patients admitted to an intensive care unit (ICU) setting [1–3]. Proton pump inhibitors (PPIs) have been found efficacious in preventing stress-related mucosal disease (also referred to as stress ulcer) bleeding (SUB) in the ICU setting, as have H2-receptor antagonists (H2RAs) [1–4]. Their comparative efficacies and the possible development of ventilator-assisted pneumonia (VAP) remain subjects of controversy with disparate data in the literature. Recent meta-analyses have suggested the superiority of PPIs [5,6], but the low incidence of SUB coupled to the high costs of this complication underline the need for a cost-effective analysis comparing PPIs with H2RAs. We therefore performed an economic analysis to better quantify the cost-effectiveness impact of these two therapeutic prophylactic approaches.

Methods

Study Population

The study population comprised patients at high risk of developing SUB in the ICU setting. These patients were identified by using the Nationwide Inpatient Sample (NIS) 2008 [7] that is supported by the Agency for Healthcare Research and Quality from the U.S. Department of Health and Human Services. This national hospitalization database comprises 8 million hospitalizations in more than 1000 hospitals located in 42 states from the United States. Hospitalizations of patients who died during the hospital stay or who were younger than 18 years were excluded from the analysis. We included only those hospitalizations that were recorded with Medicare, Medicaid, or a private insurance as the primary payer. We selected specific diagnoses to define a representative group of patients at risk of SUB. The list of all diagnoses chosen was based on the included patient populations from

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http://dx.doi.org/10.1016/j.jval.2012.08.2213
randomized trials on this topic published in the literature [8–19] and was validated by a clinician expert (A.B.). We used the principal diagnosis and 14 other possible secondary diagnoses that were expressed as International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes and the indicator of occurrence of major operating room procedure to select the hospitalizations from the NIS database. We focused on the principal diagnosis to define patient eligibility (except for septicemia that could appear as a nonprincipal diagnosis). The diagnoses were extracted from ICD-9 coding among all the available diagnoses recorded in the NIS database. The list of selected diagnoses is shown in Table 2.

Model Design

A decision tree model was constructed by using the software program TreeAge Pro Suite 2011 (TreeAge Software, Inc., Williamstown, MA) to present the use of PPIs versus H2RAs during the hospitalization for a patient at high risk of developing SUB. Treatment in the PPI group included bolus intravenous or oral omeprazole 40 mg daily. The H2RA regimen was famotidine 40 mg intravenously twice daily.

In each treatment, patients were stratified into those with complications and those with no complication. Complications were divided into two categories: SUB and VAP. The adopted time horizon was 2 months (60 days), as justified by clinical arguments below. We also adopted a third-party-payer perspective.

Probabilities

Probabilities were provided by a literature search spanning 1990 to September 2011. Computerized medical literature searches were done by using Ovid MEDLINE (1990 to September Week 2, 2011), EMBASE (1990 to 2011 Week 37), CENTRAL (fourth quarter 2011), and (ISI) Web of knowledge 4.3. All abstracts from Digestive Disease Week and United European Gastroenterology Week were also searched as were clinical trials databases [20]. Articles were selected by using a search strategy to identify reports of randomized controlled trials (RCTs) [21] with a combination of Medical Subject Headings and text words related to 1) PPI, 2) stress ulcer, 3) gastric bleeding in a, 4) clinical ill patient setting treated with either PPI, or 5) a treatment of PPIs or H2RAs. Treatment group as well as RCTs were required and three of the other aforementioned criteria for selection. Recursive searches and cross-referencing were also carried out by using a “similar articles” function; hand searches of articles were identified after an initial search. We included all adult human studies in French or English, published as full article or abstracts. Trials comparing only different dosing regimens of the same molecule were excluded. Studies assessing solely or mainly pediatric patients, or whose only outcomes were gastric pH measurements, were also excluded. All selected model probabilities were validated by an expert clinician (A.B.).

Our literature search identified 489 articles. Eight fully published articles [8–10,14–16,19,22] were included as well as five abstracts [11–13,17,18] (we evaluated the English abstract of De Azevedo et al. trial and not the full Spanish publication in keeping with the a priori limits chosen for language selection) as reported in a recently published quantitative meta-analysis by our group [23]. The resulting probabilities of SUB were 1.34% and 6.61% and those of VAP were 10.33% and 10.32% among all patients at risk for SUB following the PPI and H2RA treatments, respectively (Table 1).

Fig. 1 – Decision tree schema. H2RA, H2-receptor antagonist; P, probability; PPI, proton pump inhibitor; SUB, stress ulcer bleeding; VAP, ventilator-assisted pneumonia. Complication = SUB and VAP.

<table>
<thead>
<tr>
<th>Table 1 – Probability estimates used in the model.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability among the entire study population (%)</td>
</tr>
<tr>
<td>SUB with PPI treatment</td>
</tr>
<tr>
<td>SUB with H2RA treatment</td>
</tr>
<tr>
<td>VAP with PPI treatment</td>
</tr>
<tr>
<td>VAP with H2RA treatment</td>
</tr>
</tbody>
</table>

Notes. The only probabilities in the model are the overall complication rates (for PPI and H2RA groups), and the proportion of these that represent either an outcome of SUB or VAP. From the above, the probabilities as they appear in Figure 1 include the complication rates in the PPI arm (11.67%) and the H2RA path (16.93%), and the proportions of complications that are SUB or VAP in the PPI arm (11.5% and 88.5%) and the H2RA group (39% and 61%), respectively. Complication = SUB and VAP. All bounds were computed on the basis of 95% CI.

CI, confidence interval; H2RA, H2-receptor antagonist; PPI, proton pump inhibitor; SUB, stress ulcer bleeding; VAP, ventilator-assisted pneumonia.
**Table 2 – List of ICD-9-CM codes.**

<table>
<thead>
<tr>
<th>Category of patients</th>
<th>Category of chosen diagnosis</th>
<th>ICD-9-CM code</th>
<th>Description of the code as they appear in the ICD-9 coding system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk for SUB</td>
<td>Major trauma</td>
<td>850-854</td>
<td>Intracranial injury, excluding those with skull fracture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>860-869</td>
<td>Internal injury of thorax, abdomen, and pelvis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>925-929</td>
<td>Crushing injury</td>
</tr>
<tr>
<td></td>
<td>Hypovolemic shock</td>
<td>78559</td>
<td>Shock W/O trauma nec</td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
<td>99592</td>
<td>Sys inflam/infecti W organ dysfunct</td>
</tr>
<tr>
<td></td>
<td>Septicemia</td>
<td>0380</td>
<td>Streptococcal septicemia</td>
</tr>
<tr>
<td></td>
<td>Acute respiratory failure</td>
<td>51881</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td></td>
<td>Extensive burns</td>
<td>9483-9489</td>
<td>Burns classified according to extent of body surface involved</td>
</tr>
<tr>
<td></td>
<td>Acute renal failure</td>
<td>5846</td>
<td>Ac renal fail-cort nec</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5847</td>
<td>Ac ren fail-medull nec</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5848</td>
<td>Ac renal failure nec</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5849</td>
<td>Acute renal failure nos</td>
</tr>
<tr>
<td></td>
<td>Shock</td>
<td>5185</td>
<td>Shock lung (pulmonary insufficiency following trauma and surgery)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6395</td>
<td>Shock: circulatory collapse after complications classifiable to 630-638</td>
</tr>
<tr>
<td></td>
<td></td>
<td>66910-66914</td>
<td>Shock during or following labor and delivery (obstretric shock)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9584</td>
<td>Traumatic shock (shock following injury)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9980</td>
<td>Postoperative shock</td>
</tr>
<tr>
<td></td>
<td>Severe acute pancreatitis</td>
<td>5770</td>
<td>Diseases of pancreas acute pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Coronary artery bypass graft</td>
<td>74685</td>
<td>Coronary artery anomaly</td>
</tr>
<tr>
<td></td>
<td>surgery</td>
<td>99603</td>
<td>Due to coronary bypass graft</td>
</tr>
<tr>
<td></td>
<td></td>
<td>74685</td>
<td>Coronary artery anomaly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>99603</td>
<td>Malfunc coron bypass grf</td>
</tr>
<tr>
<td></td>
<td>Complication cases among the</td>
<td>53021</td>
<td>Ulcer of esophagus with bleeding</td>
</tr>
<tr>
<td></td>
<td>risk for SUB*</td>
<td>53100</td>
<td>Gastric ulcer: acute with hemorrhage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>53120</td>
<td>Gastric ulcer: acute with hemorrhage and perforation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>53400</td>
<td>Gastrojejunal ulcer: acute with hemorrhage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>53420</td>
<td>Gastrojejunal ulcer: acute with hemorrhage and perforation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5780</td>
<td>Gastrointestinal hemorrhage: hematemesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5781</td>
<td>Gastrointestinal hemorrhage: blood in stool</td>
</tr>
<tr>
<td></td>
<td></td>
<td>53200</td>
<td>Duodenal ulcer—acute with hemorrhage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>53220</td>
<td>Duodenal ulcer—acute with hemorrhage and perforation</td>
</tr>
<tr>
<td></td>
<td>VAP</td>
<td>99731</td>
<td>Vent assoc pneumonia</td>
</tr>
</tbody>
</table>

* The no-complication patients were defined as all the patients in the “high risk for SUB” group who were not in the SUB or VAP groups.

**Lengths of Stay and Costs**

A specific length of stay and per diem were assigned to each of the three groups of patients. Only hospital costs were included. All pharmaceutical costs were considered included in the hospital costs. Lengths of stay and costs were obtained from the NIS 2008 [7] by using a validated methodology [24] and relevant specific ICD-9-CM codes (Table 2). Two strategies were used to cost out the hospital stay of patients with complications: The VAP hospitalizations were selected among all the available diagnoses in NIS (from the 1st to the 15th diagnosis for a given patient), whereas SUB hospitalizations were selected among all the available diagnoses relating to upper gastrointestinal bleeding in NIS, excluding these when appearing as a principal diagnosis. The no-complication category was represented...
by all the patients at risk for SUB who were not in the SUB or VAP groups. In addition, only hospitalizations with major operating room procedures reported on the discharge record were considered to be eligible to represent the three subgroups of patients at risk for SUB (SUB, VAP, and no complication). Costs were computed on the basis of average charges combined with a cost-to-charge ratio, which was for the most part specific to the hospital where the hospitalization took place. More precisely, a cost-to-charge ratio specific to the hospital was used when available, and if not, a recommended group average cost-to-charge ratio was applied. Per-diem cost was the ratio of the average cost per hospitalization to the average length of stay per hospitalization. To obtain valid national cost estimates, we used discharge weights in our computation (weights were corrected to account for cases in which cost estimates were missing, as suggested by the NIS). All US$ values were expressed in 2010 US dollars by using the consumer price index for the medical care services published by the U.S. Department of Labor [25].

The diagnoses identified to represent the patient at risk for SUB and the three subgroups (SUB, VAP, and no complication) are listed in Table 2. Respecting the inclusion criteria, the weighted results present 94,865 hospitalizations in the no-complication group, 1,088 in the SUB group, and 235 in the VAP group.

In 87% of the hospitalizations that we selected from the NIS, we used a cost-to-charge specific to the hospital where the hospitalization occurred. For the other hospitalizations (where a specific cost-to-charge ratio was not available), the recommended group average cost-to-charge ratio was applied. This group average cost-to-charge ratio is defined according to several characteristics of the hospital (state, urban or rural localization, ownership of the hospital, and bedsize). By using this NIS, we found that the mean length of stay was 24 days for the SUB patients, 42 days for the VAP patients, and 14 days for the no-complication patients. Overall, a full 97.6% of the patients at risk for SUB in the NIS database were hospitalized for 60 days or fewer. This observation was clinically plausible and relevant; it justified our adoption of a 60-day time horizon for the model. The average hospitalization costs were US $41,600 (no-complication patients), US $65,500 (SUB), and US $137,700 (VAP). All costs and lengths of stay used in the model are presented in Table 3.

**Cost-Effectiveness Analysis**

The effectiveness was expressed as the probability of no complication occurring during the hospitalization. The costs were those tabulated for a complicated or uncomplicated hospital stay. The main outcome was the cost per averted complication. Results are reported as cost, effectiveness, and incremental cost-effectiveness ratio if a strategy is more effective but also more costly than another; if not, the model simply points out the strategy that is dominated (the dominated strategy is the one that is both less effective and more costly) and shows therefore the one that is preferred.

**Sensitivity and Threshold Analyses**

One-way sensitivity analyses were performed on all variables used in the model to investigate the robustness of the results and to determine which factors influence these results the most; a two-way analysis assessing pneumonia incidence in the PPI and in the H2RA treatment was also performed. Each variable was varied across its respective 95% confidence interval range. We produced a tornado diagram [27–29] to display in a single graph each of the one-way results as a single bar and to highlight which parameters have the greatest influence on the model [30].

Threshold analyses were also performed for select variables. The adoption of a willingness-to-pay threshold was arbitrary because we do not use quality-adjusted life-years (QALYs) as units of effectiveness. A probabilistic sensitivity analysis was also performed by using the Monte Carlo method [30].

**Results**

**Base-Case Analysis**

The cost-effectiveness analysis shows that the PPI strategy exhibits a US $1250 lower average cost per patient with a greater probability of not developing a complication (SUB and VAP) than the H2RA strategy. More precisely, average costs per no-complication

### Table 3 – Cost and length of stay estimates used in the model.

<table>
<thead>
<tr>
<th></th>
<th>Point estimate</th>
<th>Low bound</th>
<th>High bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per-diem cost for patients at high risk for SUB (US$, year 2010 values)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With SUB during the hospitalization</td>
<td>2764</td>
<td>2542</td>
<td>2986</td>
</tr>
<tr>
<td>With VAP</td>
<td>3310</td>
<td>3035</td>
<td>3586</td>
</tr>
<tr>
<td>No complication</td>
<td>2993</td>
<td>2915</td>
<td>3072</td>
</tr>
<tr>
<td>Length of stay (d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With SUB during the hospitalization</td>
<td>23.7</td>
<td>20</td>
<td>27</td>
</tr>
<tr>
<td>With VAP</td>
<td>41.8</td>
<td>33</td>
<td>51</td>
</tr>
<tr>
<td>No complication</td>
<td>13.9</td>
<td>13</td>
<td>15</td>
</tr>
</tbody>
</table>

Notes. Source of the point estimate: NIS2008 [7]. All bounds were computed on the basis of 95% CI. Complication = SUB and VAP.

CI, confidence interval; SUB, stress ulcer bleeding; VAP, ventilator-assisted pneumonia.

### Table 4 – Results of cost-effectiveness analysis.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost</th>
<th>Incremental cost</th>
<th>Effectiveness</th>
<th>Incremental effectiveness</th>
<th>C/E ratio</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI</td>
<td>51,849</td>
<td>0</td>
<td>0.8833</td>
<td>0</td>
<td>58,699</td>
<td>—</td>
</tr>
<tr>
<td>H2RA</td>
<td>53,099</td>
<td>1,250</td>
<td>0.8307</td>
<td>−0.0526</td>
<td>63,921</td>
<td>Dominated</td>
</tr>
</tbody>
</table>

Note. US $, year 2010 values.

C/E, cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio; PPI, proton pump inhibitor; H2RA, H2-receptor antagonist.
patient are US $58,700 for PPIs versus US $63,921 for H2RAs (Table 4). In other words, H2RAs are strictly dominated by PPIs.

**Sensitivity Analysis**

One-way sensitivity analysis

Figure 2 shows the Tornado diagram using the percentage of the variation of the base-case incremental cost-effectiveness ratio when we alter the variables inside their respective 95% confidence intervals. The probability of developing VAP is what most influences the incremental cost-effectiveness ratio. Univariate sensitivity analysis demonstrates a change in the conclusions only when varying the probability of pneumonia: H2RA ceases to be dominated if this probability (which is fixed at 10.3% in the base case for both pharmacological strategies; see Table 1) rises above 11.6% in the PPI group or if it drops below 9% in the H2RA group. Across the clinically relevant range of each of these variables, the PPI strategy becomes more expensive but remains more effective because of its greater effect on bleeding prevention.

Threshold analysis

Threshold analysis for the probability of VAP shows that only when this variable exceeds 15.6% for the PPI patients or drops below 5% for the H2RA patients does the PPI strategy become dominated. The SUB probability has to increase by more than 5% for the PPI strategy (or drop by more than 5% in the H2RA approach) for the PPI approach to lose its dominance over the H2RA strategy. Other threshold values on costs were very unlikely to occur in order to alter results in any clinically plausible way: The hospitalization cost for no complication would need to increase by more than US $1700 per day for H2RAs to become no longer dominated. Similarly, for the PPI approach to lose its dominance, the length of stay in patients with no complications or those developing SUB would need to rise by almost 60% or drop by 40%, respectively. The analysis did not identify any other threshold values.

Two-ways sensitivity analysis

Figure 3 illustrates which treatment is more cost-effective when we simultaneously vary the two probabilities of VAP in the PPI and H2RA groups. The PPI approach remains more cost-effective for an empirically set willingness to pay of US $50,000 in the majority of scenarios.

Probabilistic sensitivity analysis

A Monte-Carlo analysis was performed with 10,000 simulations assuming gamma distributions for the per-diem costs and the lengths of stay and beta distributions for all the probabilities. PPI treatment was dominant in 49% of the simulations and remained cost-effective (more effective yet more costly according to a maximum willingness to pay of US $50,000 per no complication case) in another 9% of the simulations. On average, the cost of PPI treatment was almost US $1500 lower than that of H2RA (median difference of US $3000). Similarly, the gain in mean effectiveness favored the PPI approach (88.5% vs. H2RA 83%). The corresponding cloud diagram is shown in Figure 4. The line represents the willingness-to-pay value fixed at US $50,000. Varying the willingness-to-pay line leads to the cost-acceptability curve that is shown in Figure 5.

**Discussion**

Both PPIs and H2RAs are used as antisecretory agents in a number of acid-related diseases in clinical practice [1–4]. Although cost-effectiveness models have been reported in therapeutic areas such as gastroesophageal reflux disease or in the context of peptic ulcer bleeding or a VAP. Only Schupp et al. [31] performed such an analysis, but unfortunately limited the economic outcomes to sole drug acquisition costs. As PPIs are more expensive than H2RA and simultaneously the risk of SUB is lower for
patients who receive PPIs rather than H2RAs, we felt that there were arguments for a full cost-effectiveness analysis, also providing for a more precise documentation of cost implications. Indeed, the drug costs are magnitudes smaller than the additional hospitalization costs attributable to potential complications ($15-$400 [31] vs. $65,000 for the cost of hospitalization of a bleeding complication in this patient population). Furthermore, sensitivity analyses in this cost-effectiveness report also allow us to assess the diverging associations of bleeding and pneumonia for a given pharmacological option, and the identification of possible thresholds for decision taking.

The present cost-effective analysis suggests the economic dominance of a prophylactic approach utilizing PPIs in an ICU setting compared with H2RAs. Indeed, we found that lengths of stay and per-diem costs were 14 days and US $2,993 for patients developing no complication, 24 days and US $2,764 for SUB, and 42 days and US $3,310 for VAP. Average costs per no complication were US $58,700 for PPIs and US $63,921 for H2RAs. A number of methodological decisions that can affect the interpretation of these results need to be discussed.

As it is only a subgroup of patients who are at high risk of developing SUB [32–35], we attempted to identify this target population by reviewing pertinent diagnoses and severity indices as they appeared in the NIS database, using our clinical expertise to determine such a selection (Table 2). We were unable to enter all relevant diagnoses that could represent a patient in this target population (i.e., patients who are at high risk of developing SUB) because of a lack of precision in the ICD-9 coding. We chose, however, a large number of diagnoses that emulate those of identified risk factors [36] or of previously included populations in published RCTs assessing SUB [6,37,38]. We did not identify patients simultaneously experiencing both SUB and VAP as outcomes as these would represent a very small group, and one for whom it was nearly impossible to identify relevant data in the NIS notwithstanding the possibility of synchronous complications, whereby the resulting length of stay may not be additive; these are included in the SUB or VAP complication groups in our model.
The choice of NIS assured us of a broad generalizability of results with regard to not only geographic variation but also the contemporary nature of care [7].

We chose a decision tree approach as the best way to model the decisional impact of treating patients at risk for SUB [39–42], considering the short clinically pertinent time horizon and the chosen outcome [43]. Furthermore, because there was no necessity to focus on recurrent health states involving back and forth movements in the time, decision tree appeared more indicated than opting for a Markov model [44].

There exist no QALYs described for this condition to the best of our knowledge. The choice of the unit of effectiveness of cost per averted complication is in keeping with the nature of the medical complications that are self-limited, and usually devoid of prolonged impact beyond the 60-day time horizon. If the outcome of bleeding or pneumonia is now an unusual one, bleeding or pneumonia-related mortality represents only a proportion of these rates, with an even smaller number of patients, thus limiting its choice as an outcome of interest. The chosen outcome of averted complication is in keeping with other cost-effectiveness analyses of similar short-term clinical outcomes [39,45–48] and is in keeping with methodological suggestions published in the literature [27,49].

We did not model for a strategy that used sucralfate in our analysis because this medication is an older, now little used method of SUB prophylaxis. Furthermore, some comparative trials, most of which date back up to 21 years (close to the start of intravenous PPI availability), can be misleading as there have been major advances in supportive care that have significantly decreased SUB and VAP, as further discussed below. An exploratory analysis that included all three prophylactic strategies (PPI, H2RA, and sucralfate) did not alter the findings of PPI dominance [50]. We do not include these data as we feel they are less clinically useful for the aforementioned reasons, and may even be misleading with regard to the final estimates of costs and effectiveness. Although there exist wide clinical heterogeneity in the RCTs, our probability assumptions are taken from the available contemporary literature [8–18,32,51–61], including a recent robust meta-analysis [38]; we did include all relevant trials. Table 3 reports a per-diem hospitalization cost of US $2993 for no-complication patients and US $2764 for patients with SUB during their hospitalization. Although counterintuitive, because the first days of a hospitalization usually require more medical and human resources, the per-diem cost is lower for patients with longer hospitalizations, as is the case for patients who develop complications during hospitalization. Of course, the total hospitalization costs are greater for this group (due to the markedly greater length of stay). This has been previously reported [24].

Additional choices of point-estimates also deserve discussion: the PPI and H2RA treatment strategies were associated with SUB and VAP probabilities of 1.34% and 6.61% and 10.33% and 10.32%, respectively. Higher VAP rates can be found in the literature: Eom et al. [62] computed a risk of 19.3% for patients treated with H2RAs. Contrarily to our more contemporary estimates, however, this research group included in their calculations trials as old as 1985. We did not consider such older studies as it is well accepted that VAP rates have decreased significantly in more recent years [13,15,18,19]. Even though our conclusions are sensitive to VAP rate estimations, the adopted confidence intervals we use are already very wide (7%–14%) given the contemporary practice of medicine [13,15,18,19].

To ensure the robustness of the results, we performed many sensitivity analyses. One-way sensitivity analysis was performed to explore the impact of the different assumptions across their broad adopted ranges on the results of the model (also in keeping with ISPOR recommendations [27]). Two-way analysis varying both the SUB and VAP probabilities synchronously confirmed the robustness of the conclusions. Probabilistic sensitivity analysis additionally tested the uncertainty of all variables simultaneously across 10,000 simulations of the model. The resulting cost-acceptability curve showed how the willingness to pay failed to have a significant impact on the strategic choice. Threshold analyses suggested that only clinically irrelevant values could alter these conclusions.

The plotting of cost-acceptability curves remains complex and somewhat subjective whatever the outcome as disparate willingness-to-pay thresholds are reported in the literature [63–67]. Furthermore, we could not use a reference based on willingness to pay per QALY because we did not adopt QALYs as units of effectiveness. The nearest content-relevant examples we could find were those of Enns et al. [39] who worked with a willingness to pay per rebleed averted and Briggs et al. [68] who adopted a willingness to pay per no gastroesophageal reflux disease symptoms. There are no references in the literature for a willingness to pay per complication averted in the context of SUB prophylaxis [39] that we could find. Ubel et al. [67] suggest that the choices of willingness to pay usually are underestimates among published cost-effectiveness analyses, at least as it pertains to the use of QALYs as a measure of effectiveness. We, therefore, granted arbitrarily as most, fixed a cutoff point at US $50,000. This value is consistent with the order of magnitude of the average cost of treatment as noted in our analysis, as shown have suggested to do [39,67,68].

**Conclusion**

Based on available current data both from RCTs and from a large contemporary observational administrative database informing our probability and cost estimates, a strategy of PPI prophylaxis is the most efficient approach in patients at high risk of developing SUB when compared with using H2RAs.

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