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Jeremy M. Kahn
Jason N. Doctor
Gordon D. Rubenfeld

Stress ulcer prophylaxis in mechanically ventilated patients: integrating evidence and judgment using a decision analysis

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J. M. Kahn · G. D. Rubenfeld (✉)
Harborview Medical Center, Division of Pulmonary and Critical Care Medicine,
325 Ninth Avenue, 359762, Seattle 98119, WA, USA
e-mail: nodrog@u.washington.edu
Tel.: +1-206-7313356
Fax: +1-206-7318584

J. N. Doctor
University of Washington, Department of Medical Education and Biomedical Informatics,
1959 NE Pacific Street, 357240, Seattle 98195, WA, USA

Abstract *Objective:* Stress ulcer prophylaxis with a histamine-2 receptor antagonist can reduce the risk of gastrointestinal bleeding in mechanically ventilated patients but may also increase the risk of ventilator-associated pneumonia. We sought to clarify the tradeoffs involved in selecting a prophylactic strategy. *Design:* Decision analysis. *Patients and participants:* A decision tree was constructed for a hypothetical cohort of patients receiving mechanical ventilation for an expected duration of longer than 48 h, using probabilities estimated from the published literature. *Interventions:* Patients in the model could receive either prophylaxis with a histamine-2 receptor antagonist or no prophylaxis. Sensitivity analyses were preformed varying the estimated probabilities over their plausible ranges. *Measurements and results:* Both strategies were associated with approximately the same baseline expected mortality (16.6% for histamine-2 receptor antagonists and 16.9% for no prophylaxis, risk difference 0.3%). Varying the estimated probabilities resulted in only small changes in both the expected mortality and the absolute risk reduction associated with the preferred treatment. At the extremes of assumptions the absolute mortality reduction ranged from 0.1% to 3.3%. *Conclusions:* No single strategy of stress ulcer prophylaxis is preferred when mortality is used as the outcome. In the absence of a clinical trial demonstrating survival benefit the individual clinician's assumptions regarding the effect of prophylaxis on gastrointestinal bleeding and pneumonia and the attributable mortality of pneumonia vs. gastrointestinal bleeding will have a significant effect on the decision.

Keywords Critical care · Intensive care · Gastrointestinal hemorrhage · Pneumonia · Nosocomial infections

Introduction

Stress ulcer prophylaxis is commonly used in patients receiving mechanical ventilation to prevent clinically significant gastrointestinal (GI) bleeding (GIB) [1]. Despite over 50 randomized trials and several meta-analyses, however, the optimal strategy for stress ulcer prophylaxis remains controversial and practice patterns vary widely across providers [2, 3, 4, 5, 6]. One reason for this is that no clinical trial of stress ulcer prophylaxis has demonstrated a statistically significant reduction in mortality or length of stay, raising the question of whether any ultimate patient benefit is provided. The decision is further complicated by evidence suggesting that histamine receptor-2 (H2) antagonists, the most common agents used for prophylaxis, may increase the risk of ventilator-associated pneumonia (VAP) [7, 8]. Clinicians deciding whether to provide prophylaxis for ventilated patients must therefore balance the competing risks of GIB and VAP.

The absence of an optimal strategy for stress ulcer prophylaxis is reflected in the lack of consensus among current position statements and systematic reviews. Guide-

lines on the prevention of VAP, for instance, highlight the increased risk of pneumonia associated with prophylaxis and the importance of patient selection but avoid specific recommendations [9, 10, 11, 12]. The United States Agency for Health Care Research and Quality (AHRQ) patient safety report states that "physicians may consider use of prophylactic agents . . . to prevent clinically important GIB in very high-risk patients admitted to the ICU. However, the risk of pneumonia may influence clinicians to use prophylactic agents only in patients with multiple risk factors for GIB, and simply provide enteral nutrition to others at less risk" [13]. A guideline developed by the American Thoracic Society is similarly vague, stating that "if stress ulcer prophylaxis is indicated, the risks and benefits of each regimen should be weighed before prescribing either H2 blockers or sucralfate" [12]. Other guidelines attempt to resolve this controversy simply by recommending prophylaxis for all ventilated patients regardless of risk, but without specifying which agent to use [14, 15, 16].

When evidence is not persuasive, clinicians must make decisions based on their own assessments of the treatment's risks and benefits [17]. The purpose of this study was to explore a decision in a common scenario where the evidence of effect on mortality is not compelling and the decision is clouded by competing risks. A decision analysis was used to assess the effects of varying the assumptions about the relative efficacy and risks of prophylaxis on outcome. We hypothesized that the lack of clear practice guidelines and wide practice variation in the area of stress ulcer prophylaxis could be explained by incorporating different assumptions about the above variables into the decision.

Materials and methods

Overview of the decision model

We constructed a decision tree for a hypothetical cohort of patients in a multidisciplinary ICU receiving mechanical ventilation for an anticipated duration of longer than 48 h (TreeAge Pro 2005, TreeAge Software, Williamstown, Mass., USA). The decision was for one of two different strategies initiated on admission: prophylaxis with an intravenous H2-antagonist or no prophylaxis. Sucralfate was not included in the analysis since two randomized trials have shown sucralfate to be inferior to H2 antagonists and not significantly different than placebo in prevention of clinically important GIB [18, 19]. Proton pump inhibitors (PPIs) were also not included, as three randomized trials have shown that they are not superior to H2 antagonists at preventing GIB [20, 21, 22]. Patients in the model could experience two exclusive complications of mechanical ventilation: a clinically significant (rather than endoscopically proven) GIB or VAP or no complication. The outcome was in-hospital mortality.

Model inputs

Six risks were used in the model: the baseline risk of GIB and VAP, the relative risk of GIB and VAP after prophylaxis with H2 antagonists, and the relative risk of hospital death after each complication (Table 1). The relative risks of GIB and VAP associated with prophylaxis were taken from two recent meta-analyses [2, 3]. The baseline risks of VAP and GIB and the risk of death after these complications were estimated from articles obtained in two separate Medline searches. The first used the terms "stress ulcer" and "intensive care unit" and the second used the term "ventilator-associated pneumonia." Results were narrowed to English language studies pertaining to adults, resulting in 55 articles potentially pertaining to GIB and 359 articles potentially pertaining to VAP. Titles and abstracts were reviewed for significance to the topic. The full text of relevant articles was reviewed for observational cohort studies that defined the exposure and presented incidence data or risk estimates associating VAP or GIB with mortality. Bibliographies and review articles were examined to identify sources potentially missed by the Medline search. The final search yielded six articles on the incidence and outcome of stress ulcer-associated GIB [23, 24, 25, 26, 27, 28] and 12 articles on the incidence and outcome of VAP [29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40]. Based on the literature review all risks were assigned a point estimate for the base-case analysis as well a range of plausible values. A baseline risk of death of 15% was assigned for those not experiencing GIB or VAP.

Tree evaluation and sensitivity analysis

The decision tree was evaluated both by determining the preferred strategy under the given assumptions (the strategy with the lowest expected mortality) and by determining the absolute risk reduction associated with

Table 1 Model inputs. Each point estimate is associated with a range of plausible values for use in the sensitivity analysis (*GIB* gastrointestinal bleeding, *VAP* ventilator-associated pneumonia, *RR* relative risk)

Input	Base case value	References
GIB risk	6% (0–15%)	[23–28]
VAP risk	15% (5–60%)	[29–40]
RR of death from GIB	2.33 (1.0–2.5)	[23, 26]
RR of death from VAP	1.33 (1.0–2.0)	[31–40]
RR of GIB from prophylaxis	0.50 (0.22–1.0)	[2, 3]
RR of VAP from prophylaxis	1.33 (1.0–2.0)	[2, 3]

Table 2 Four hypothetical mechanically ventilated patients used in the two-way sensitivity analysis; probabilities estimated using logistic models from the published literature [23, 30] (*GIB* gastrointestinal bleeding, *VAP* ventilator-associated pneumonia)

Patient	Description	Clinical scenario	GIB risk (%)	VAP risk (%)
A	Low GIB risk, low VAP risk	Uncomplicated hospital-acquired pneumonia, receiving intravenous antibiotics	1	7
B	Low GIB risk, high VAP risk	Severe acute respiratory distress syndrome, receiving neuromuscular blockade	1	30
C	High GIB risk, low VAP risk	Pancreatitis, vasodilatory shock, coagulopathy, receiving intravenous antibiotics	12	12
D	High GIB risk, high VAP risk	Meningitis complicated by seizure, witnessed aspiration, receiving corticosteriods	9	41

the preferred strategy (the difference in the expected mortality between the two decisions). Thus we were able to assess not only which strategy was preferred but also the magnitude of the effect under which that strategy was preferred. A multivariate probabilistic sensitivity analysis was performed by conducting a Monte Carlo simulation for 1,000 patients in which the clinical probabilities were randomly sampled from distributions approximating the means and ranges in Table 1 [41]. The central 95% range from the simulation provides an approximation of 95% confidence intervals for the expected mortalities and risk differences. One- and two-way sensitivity analyses were also performed to examine the effects of varying the individual assumptions on both the preferred strategy and the absolute risk reduction. Ideally we would present three-way sensitivity analyses varying all important risks simultaneously. Because such analyses would be difficult to present and interpret, we instead chose to present four two-way sensitivity analyses based upon clinically relevant hypothetical scenarios (Table 2). These scenarios represent specific patients with varying degrees of baseline risk for VAP and GIB, estimated by generating predictive logistic models using odds ratios in the published literature [23, 30]. Scenarios with lower baseline risks of VAP show the effect of GI prophylaxis in the setting of interventions that might prevent VAP such as semirecumbent positioning and selective decontamination of the digestive tract [11].

Results

Base-case and probabilistic sensitivity analysis

After evaluating the tree using the baseline risk estimates both stress ulcer prophylaxis strategies were associated with approximately the same risk of death. H2 antagonists were associated with 16.6% expected mortality (95% range from multivariate probabilistic sensitivity analysis, 15.7–17.5%). A strategy of no prophylaxis was associated with 16.9% expected mortality (95% range, 15.9–18.0%). The absolute risk difference favoring H2 antagonists was 0.3% (95% range, 0.3–0.9%).

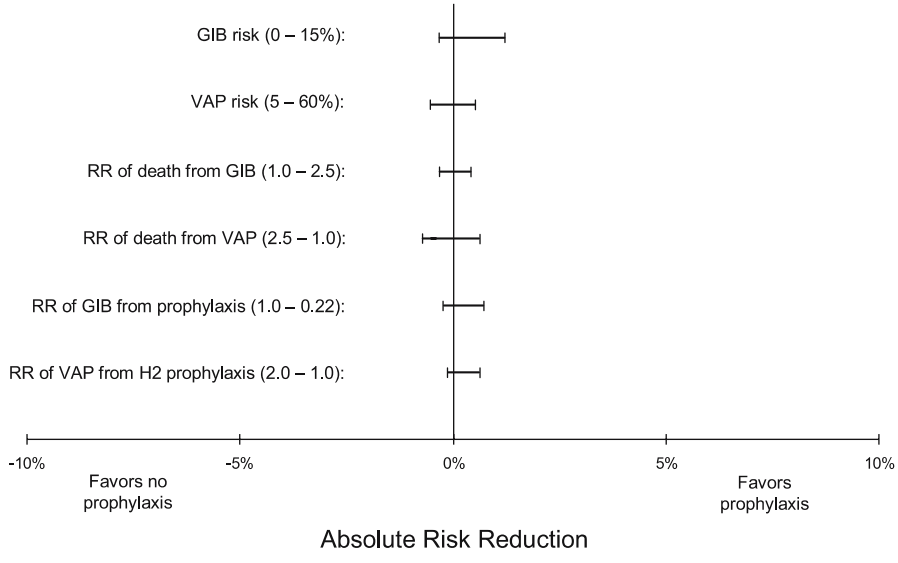

Fig. 1 One-way sensitivity analysis for the absolute mortality risk reduction associated with the preferred treatment. *GIB* Gastrointestinal bleeding; *VAP* ventilator-associated pneumonia; *RR* relative risk

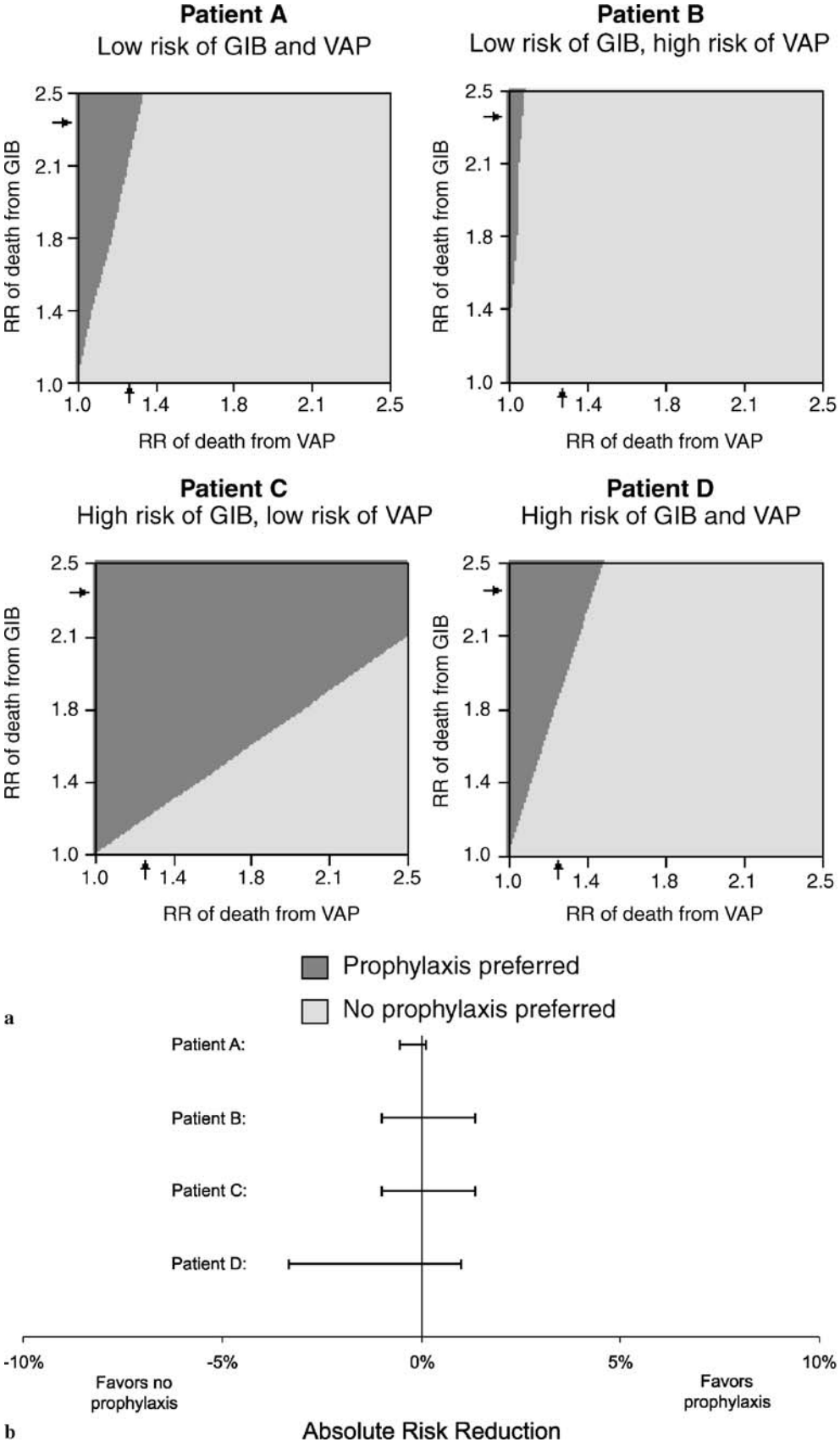

Fig. 2 **a** Two-way sensitivity analysis of mortality from gastrointestinal bleeding (*GIB*) mortality vs. that from ventilator-associated pneumonia (*VAP*) in four hypothetical patients. *Shaded areas* correspond to clinical scenarios in which the indicated prophylactic strategy results in the lower expected mortality; *arrows* base case assumptions. *RR* Relative risk. **b** Absolute mortality risk reduction from two-way sensitivity analysis of GIB mortality vs. VAP mortality in four hypothetical patients at the extremes of assumptions. *Left side border of each bar* Absolute risk reduction given the assumptions that GIB has no effect on mortality (RR = 1.0), and that VAP has a large effect on mortality (RR = 2.5); *right border of each bar* absolute risk reduction given the assumptions that GIB has a large effect on mortality (RR = 2.5), and that VAP has no effect on mortality (RR = 1.0)

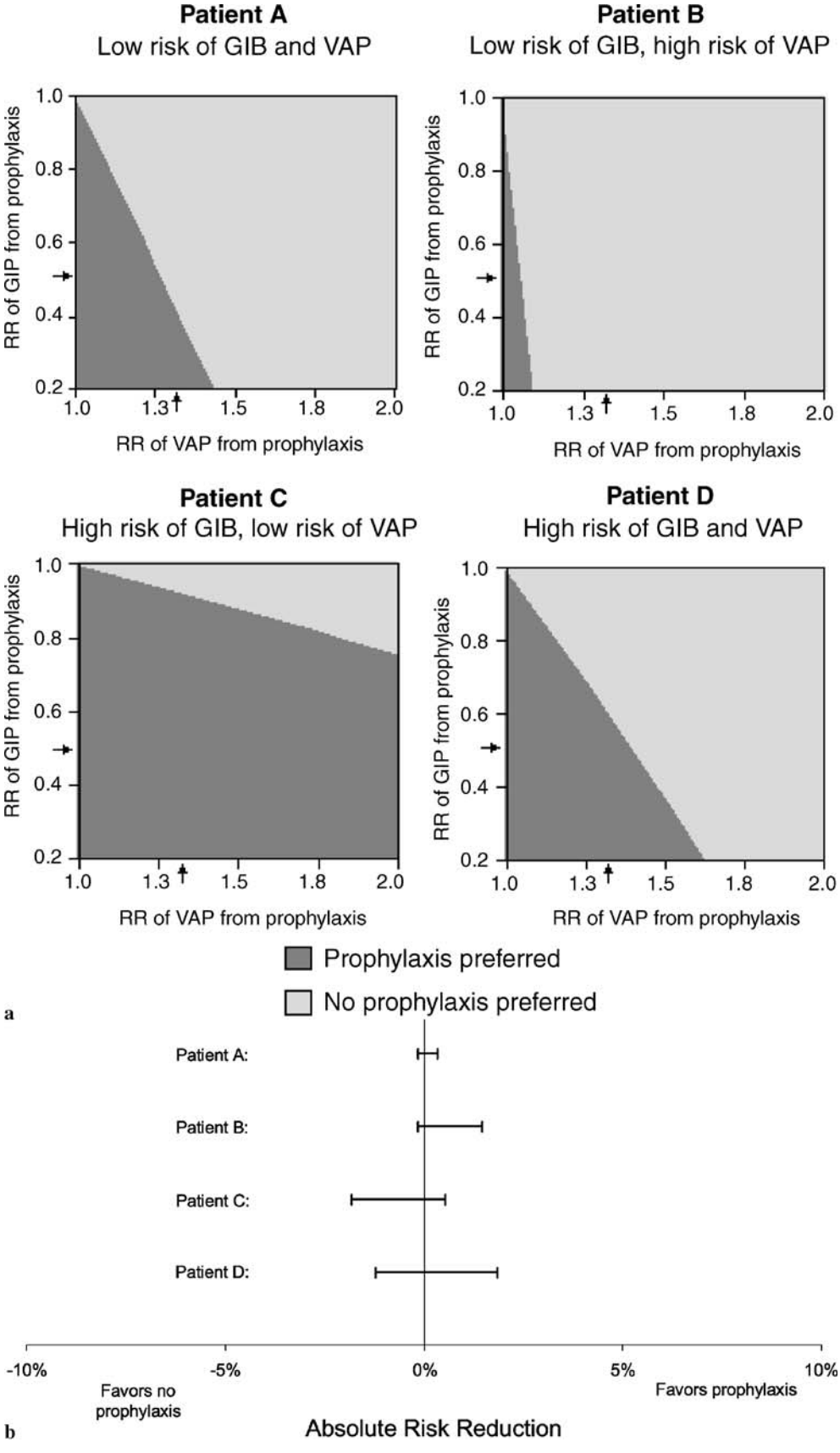

Fig. 3 **a** Two-way sensitivity analysis of efficacy of prophylaxis at preventing gastrointestinal bleeding (*GIB*) vs. risk of ventilator-associated pneumonia (*VAP*) related to prophylaxis. *Shaded areas* correspond to clinical scenarios in which the indicated prophylactic strategy results in the lower expected mortality; *arrows* base case assumptions. *RR* Relative risk. **b** Absolute mortality risk reduction from two-way sensitivity analysis of risk/efficacy for four hypothetical patients at extremes of assumptions. *Left side border of each bar* Absolute risk reduction given the assumptions that prophylaxis has no effect on GIB risk (RR = 1.0) and has a large effect on VAP risk (RR = 2.0); *right side border of each bar* absolute risk reduction given the assumptions that prophylaxis has a large effect on GIB risk (RR = 0.2) and has no effect on VAP risk (RR = 1.0)

One-way sensitivity analysis

A one-way sensitivity was then performed to determine the absolute risk reduction associated with the preferred treatment strategy when the individual assumptions are varied (Fig. 1). Even at the extremes of assumptions for each variable, the absolute risk reduction associated with the preferred prophylaxis strategy was small. For example, prophylaxis is favored at higher GIB risks, but even when the risk is extremely high (15%) the absolute risk reduction in mortality associated with prophylaxis is only 1.2%. Furthermore, if one assumes that VAP increases mortality 2.5-fold, then the decision not to provide prophylaxis conveys an absolute risk increase of only 0.7%. For the other variables the absolute risk reductions are all similarly small, less than 1% at the extremes of assumptions.

Two-way sensitivity analysis

Two-way sensitivity analyses were performed for each of the four hypothetical patients representing varying baseline risks of GIB and VAP. Figure 2 shows the results of varying the assumptions about the effect of GIB and VAP on hospital mortality with regards to the preferred strategy (Fig. 2a) and the associated absolute risk reduction (Fig. 2b). Increasing the risk of death from GIB favors a strategy of prophylaxis, while increasing the risk of death from VAP favors a strategy of no prophylaxis. Both strategies, however, are supported across the range of plausible assumptions about the morbidity of GIB and VAP. Only in one of the four patients (patient B, with a low risk of bleeding and high risk of VAP) is one of the strategies (no prophylaxis) preferred across most assumptions. Importantly, at the extremes of assumptions the absolute risk reduction associated with the preferred strategy remains relatively small. Only under the assumptions of high GIB and VAP risk (patient D), no effect of GIB on ortality, and a 2.5-fold increase in mortality attributed to VAP is any absolute risk reduction greater than 1.5%. In this extreme combination of assumptions, the absolute risk reduction favoring no prophylaxis is 3.3%.

Figure 3 shows the results of varying the assumptions about the relative efficacy of stress ulcer prophylaxis in preventing GIB and the relative risk of stress ulcer prophylaxis in causing VAP with regards to the preferred strategy (Fig. 3a) and the associated absolute risk reduction (Fig. 3b). Increasing the effectiveness of H2 antagonists at preventing GIB favors a strategy of stress ulcer prophylaxis, while increasing the risk of VAP from stress ulcer prophylaxis favors a strategy of no prophylaxis. Both decisions are supported within the range of plausible assumptions about the variables for all four patients. Even at the extremes of assumptions, the preferred decision is associated with only small reductions in the absolute risk of death. Similar to the previous analysis, the largest effect on mortality is seen under the conditions of high GIB and VAP risk (patient D), no effect of stress ulcer prophylaxis on VAP, and a large protective effect on GIB (relative risk 0.2). In this extreme case the absolute risk reduction favoring prophylaxis is 1.9%.

Discussion

We demonstrate that given the available evidence the decision to provide stress ulcer prophylaxis across a range of assumptions is one of general equivalence. Both H2 antagonists and no prophylaxis were associated with roughly the same expected mortality under the base case assumptions. Varying these assumptions over a wide range of plausible values resulted in different preferred decisions, but the absolute differences in mortality, even at the extremes, remained small. Either providing or not providing prophylaxis was validly supported by reasonable assumptions about the epidemiology of GIB and VAP, indicating that the evidence supports a broad range of practice patterns.

This analysis has important implications for the care of mechanically ventilated patients and for evidence-based decision making in the ICU. It explains why despite over 50 randomized trials and two well-conducted meta-analyses there are no specific guidelines for stress ulcer prophylaxis in ventilated patients [10, 11, 12, 13]. As we demonstrate, with the exception of scenarios at the extremes justified by the literature, the expected effect on mortality of providing stress ulcer prophylaxis is small. In most cases there is no significant effect on mortality. Thus even with such a large body of literature, there is little justification for a broad-based guideline recommending prophylaxis even for subsets of the population at risk.

This analysis also has implications for the use of stress ulcer prophylaxis as a quality of care measure in the ICU. Currently the Joint Commission on Accreditation of Healthcare Organizations and the Institute for Healthcare Improvement recommend universal stress ulcer prophylaxis as a core quality measure for mechanically ventilated patients [15, 16]. We have demonstrated that given the competing risks stress ulcer prophylaxis actually has minimal impact on mortality, and an evidence-based clinician might reasonably choose not to provide prophylaxis. In the absence of a clinical trial evidence linking stress ulcer prophylaxis with mortality or length of stay the use of stress ulcer prophylaxis rates as an ICU quality indicator is premature.

Whenever the data on treatment efficacy for clinically important outcomes are not compelling, clinicians must inform their decisions by making assumptions about treatment and disease [42, 43]. When these assumptions vary across providers, different clinicians will reach different conclusions about the best decision. In this study we have shown how the decision to use stress ulcer prophylaxis in

the ICU is influenced by these assumptions. The evidence for using stress ulcer prophylaxis is uncertain because GIB is rare, the potential effect of prophylaxis on VAP and GIB is small, and no mortality benefit has been demonstrated for prophylaxis. To arrive at an evidence-based decision for an individual patient clinicians must therefore combine clinical trial data showing the effect on secondary endpoints and epidemiological data showing the effect of that endpoint on mortality. This means incorporating multiple factors, including the baseline risk of GIB and pneumonia, the effect of prophylaxis on bleeding and pneumonia, and the relative effect of bleeding and pneumonia on outcome. The fact that different physicians have different assumptions about these variables means that the decision is likely to vary significantly across providers.

Our analysis has several limitations. For one, it does not account for the ability of a patient to experience both GIB and VAP or one complication twice. Similarly, it does not account for potential interaction between the two outcomes, such that a patient with VAP may be at higher risk for GIB. A full account of the interaction between these two complications would require more complicated models such as a Markov model, which allow patients to experience all potential complications as well as repeat complications. What is gained in accuracy in this type of model, however, is lost in simplicity and opacity. Additionally, given the lack of current data on the interaction between GIB and VAP and the fact that both are heavily dependent on the length of mechanical ventilation, we did not feel it would be possible to estimate all the necessary probabilities for such a model in an unbiased fashion. Another limitation is that costs were not evaluated. Factors influencing costs such as length of stay, endoscopic interventions for GIB and discharge location are extremely variable across institutions, limiting the ability to generalize the results of a cost analysis. Finally, we did not include a separate analysis of PPIs or sucralfate. Sucralfate's effect can be estimated by the performance of the placebo group in this model as it has not been shown to be different than placebo in preventing GIB [18]. The effect of PPIs can be estimated by the performance of the H2 antagonists group. Although used by some ICU providers for stress ulcer prophylaxis, no published studies have shown PPIs to be superior to H2 antagonists in prevention of GIB [20, 21, 22]. PPIs have also been shown to significantly raise gastric pHcompared to H2 antagonists, which may result in a greater risk of pneumonia [8]. This potential effect is captured in the sensitivity analysis for H2 antagonists.

Conclusions

The lack of consensus regarding optimal prophylaxis strategy is likely due to uncertainty in the evidence and variation in individual clinician assumptions about the effects of prophylaxis on GIB and pneumonia and the relationship of these complications to mortality. This decision analysis shows how varying these assumptions leads to different conclusions regarding the preferred treatment strategy. Clinicians can use this study to better inform the way evidence is integrated with judgment in medical decision making.

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