IRB Proposal
Incidence of VAP associated with gastric ulcer prophylaxis: PPIs vs H2RA.
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1. Study Purpose and Rationale.

Ventilated patients maintained in an ICU setting are at increased risk for mucosal bleeding for a variety of reasons, including stress-induced hypercortisolemia, use of parenteral nutrition, and coagulopathy[1]. Gastric acid-reducing therapy is indicated for primary prevention of gastrointestinal ulcers in most ICU patients[2], and is a standard intervention in "ventilator bundles" at our hospital among many others. However, previous studies have indicated that effective ulcer prophylaxis comes at a cost of an increased incidence of ventilator-associated pneumonias (VAPs)[3]. VAP occurs in 8-28% of ventilated patients, and carries a mortality risk of 24-50%[4]. These iatrogenic infections account for a large burden of morbidity, mortality, and health care costs.

The ideal regimen of ulcer prophylaxis is not clearly delineated. A limited number of studies[5] have indicated similar efficacy between histamine receptor antagonists (H2RAs) and proton-pump inhibitors (PPIs), a newer class of medications. In a diverse population consisting of both community and hospital patients, an increased incidence of pneumonia has been associated with PPI use compared with H2RAs[6]; conversely, a retrospective analysis of a surgical ICU population demonstrated no increase in the incidence of VAPs[7]. We propose to randomize ventilated ICU patients to ranitidine, an H2RA, or omeprazole, a PPI, to observe the incidence of VAP, in an effort to better characterize a preferred ulcer prophylaxis regimen.

2. Study Design and Statistical Procedures.

The primary endpoint of interest will be the clinical diagnosis of VAP and associated initiation of empiric antibiotic therapy. Secondary endpoints will include the incidence of significant gastrointestinal bleeding (defined as 2 g/dl drop in hemoglobin with hemoccult testing positive and no other evidence of active bleeding to account for the drop) and 90-day all-cause mortality. Exclusion criteria will include prior randomization in this trial, ventilator time less than 48 hours, current diagnosis of pneumonia, or history of GIB in the previous 180 days.

We estimate that with enrollment of 962 subjects in each group, the study would have 80% power to detect an increase of 5% in the PPI group from a baseline VAP incidence of 15% in the H2RA group. The level of alpha error is set at 0.05.

Data will be analyzed on intent to treat basis, excluding those patients who are maintained on the ventilator for less that 48 hours. A Kaplan-Meier curve will be constructed with number of patients at risk. Subjects will be included until the end of the

14^{th} day of mechanical ventilation, at which point the will be considered to have not developed VAP.

3. Study Procedures

Informed consent will be obtained from all patients who are able to give it. However, we expect many subjects in our study population to be unable to provide consent; therefore, we will obtain surrogate consent from health-care proxies, or the most immediate surrogate, if no health care proxy has been designated.

Once informed consent is obtained, patients intubated during the same hospitalization (including by EMT personnel in the field, the ED, on the floor, or in the ICU) will be randomized to either 150mg daily of ranitidine or 40mg daily of omeprazole in a blinded fashion. The study drug may be administered either IV, via NG or PEG tube as indicated by the clinical context and as decided by the primary team. There will be no placebo. The subject will be maintained on therapy as long as he or she is intubated. Study drug may be withdrawn or changed at any time by the treating team at their discretion. A new GIB will qualify as meeting an endpoint; study drug will be discontinued, and active GIB therapy will be instituted (including IV PPI).

4. Study Drugs or Devices

H2RAs work by inhibiting communication between gastric ECL cells, which receive enteric innervation, and parietal cells of the stomach, which secrete acid. Decreased stimulation at the histaminic receptor on parietal cells leads to a decrease in intracellular cAMP, which in turn inhibits the action of a luminal hydrogen-potassium ATPase (H^+K^+-ATPase). This decrease in signaling can be overcome by parallel pathways, including gastrin (a enteric hormone) secretion.

PPIs act inside the parietal cell; they covalently bind the H^+K^+-ATPase and irreversibly deactivate it.

Clinical experience has shown that PPIs produce stronger acid suppression, raise gastric pH more towards neutrality, and are more difficult to overcome via parallel mechanisms (the H^+K^+-ATPase is the final common pathway of gastric acid secretion) than H2RA.

5. Study Questionnaires

Not applicable.

6. Study Subjects.

The cohort from which we will draw our population consists of all patients admitted to the medical ICU dependent upon mechanical ventilation.

Inclusion Criteria:
- Age >17
- intubated during current admission
- receive mechanical ventilation for >48 hours

Exclusion Criteria
- Previous randomization in this study
- Confirmed GIB in past 180 days
- Current confirmed or suspected pneumonia
- allergy to either of study drugs
- known esophageal varicies

VAP will be diagnosed using the CDC guidelines for diagnosis of VAP[8]. A diagnosis of VAP will be valid up to 48 hours after withdrawal of mechanical ventilation should pneumonia develop.

7. Recruitment

Every patient sustained on mechanical ventilation admitted to the ICU (or their proxy) will be approached by their treating physician to determine if they might be interested in participating. No advertisements, private practices or clinics will be involved.

8. Confidentiality of Study Data

Subjects will be assigned a study number. Study data will be collected and stored in a password-protected electronic database. All patient identifiers will be stored in a separate file that includes subject number. Only the principle investigator and his or her research staff will have access to the database.

9. Potential Risks

The known risks associated with acid reduction therapy include most prominently the anticipated outcome, that is, an increase in VAP. However, current clinical practice believes that the risk of increased incidence of VAP is outweighed by the benefit of decreasing life-threatening gastric mucosal bleeds. The risk that one acid reduction therapy is superior to another in preventing ulcers, while theoretically possible, has not been borne out by previous studies.

10. Potential Benefits

There are no expected direct benefits to the patients in this study. Other ventilated patients may receive a benefit in the future if one group has a lower incidence of VAP.

11. Alternatives

The alternative is to not participate in this study. Care will be provided by the primary team according to current practice without regard to participation status.

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4. Chastre J, Fagon J-Y. Ventilator-associated pneumonia. *American Journal of Respiratory & Critical Care Medicine.*165(7):867-903.

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