Descriptive Analysis of a Clinical Pharmacy Intervention to Improve the Appropriate Use of Stress Ulcer Prophylaxis in a Hospital Infectious Disease Ward

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ABSTRACT

BACKGROUND: Stress ulcers are acute superficial inflammatory lesions of the gastric mucosa induced when an individual is subjected to unusually high physiologic demands. In recent years, use of acid suppression therapy (AST) for stress ulcer prophylaxis (SUP) in inpatient settings other than intensive care has become increasingly common, leading to increased drug cost and an avoidable increased risk of adverse events such as hospital-acquired pneumonia.

OBJECTIVE: To assess the effects of a clinical pharmacist intervention including AST prescribing and adherence to a SUP guideline that was developed by clinical pharmacists for use in the infectious disease ward of a teaching hospital based on the 1999 American Society of Health-System Pharmacists (ASHP) guidelines for use of SUP.

METHODS: This was an exploratory, prospective pre- and post-intervention study of all patients admitted to the infectious disease ward of Imam Khomeini Hospital, the major referral hospital for infectious disease patients in Iran, which is affiliated with Tehran University of Medical Sciences. The study intervention consisted of the use of an internal guideline for SUP that was prepared by clinical pharmacists in accordance with ASHP guidelines, followed by education provided to the physicians who monitored and visited the hospitalized patients in the infectious disease ward. For the 4-month pre-intervention (August 1, 2008, to December 1, 2008) and post-intervention (February 1, 2009, to June 1, 2009) periods, the following data were collected: admitting diagnoses, number and type of SUP risk factors for AST, and type of AST medication used (omeprazole or ranitidine). Exclusions included (a) patients using AST for appropriate gastrointestinal diagnoses at admission (n = 4 in each period), and (b) patients who died during the hospital stay because of a cause other than gastrointestinal diagnoses at admission (n = 4 in each period), and (b) patients ranitidine). 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What is already known about this subject

- Several trials have demonstrated the inappropriate use of acid suppressive therapy (AST) in general medicine patients based on current recommendations. The frequency of AST use in general medicine patients reported in the literature is approximately 70%. Ranitidine or other histamine2-receptor antagonists along with proton pump inhibitors (PPIs) are the most frequently prescribed agents in most studies. Most patients in these studies had inappropriate indications for AST, and the continued unnecessary use after discharge is a concern.

- The development of institution-specific guidelines is recommended to identify the most appropriate candidates for receipt of stress ulcer prophylaxis (SUP). The American Society of Health-System Pharmacists (ASHP) therapeutic guidelines on SUP, with the update by Allen et al. (2004), are commonly used as the basis for development of institution-specific guidelines. Adherence to these recommendations is less than ideal, particularly in settings other than the intensive care unit (ICU). There is often insufficient support for the use of SUP in non-ICU settings.

- The ASHP guidelines on SUP are based in part on evidence published by Cook et al. (1994) in which 2 significant risk factors were identified for stress-induced bleeding: mechanical ventilation or coagulopathy. A history of gastrointestinal bleeding is also considered as an indicator for SUP. However, the frequency of clinically important bleeding is low, and patients should be assessed prior to receiving AST according to institution-specific guidelines to determine the relative (optional) and absolute risk factors for gastrointestinal bleeding.
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What this study adds

- A pre- and post-intervention study design without a comparison group found that a treatment guideline for SUP introduced by clinical pharmacists in a non-ICU setting was associated with a reduction in overall use of AST from 80.9% of patients in the pre-intervention period to 47.1% in the post-intervention period. However, there was no significant change in the underuse of AST in patients with an indication for SUP (21.7% in the pre-intervention period vs. 14.3% in the post-intervention period) or in the proportion of patients who received AST without an indication for SUP (91.5% in the pre-intervention period vs. 89.4% in the post-intervention period).

Methods

The infectious disease ward of Imam Khomeini Hospital developed a pharmacist-directed infectious disease management program in 2001. The Pharmaceutical Care Clinic was established as a way to standardize the treatment of infectious disease patients within this ward by incorporating the pharmacists who are specialists in this subdivision of clinical practice. The pharmacists in the Pharmaceutical Care Clinic work in collaborative practice with physicians, making recommendations for ordering laboratory tests, initiating medications, and changing the prescribed medications or the orders associated with them.

This present study was conducted prospectively from August 2008 to June 2009 in the infectious disease ward of Imam Khomeini Hospital. All patients admitted to this ward during this time were eligible for inclusion in the present study. The study period was divided in 2 parts. During the first 4 months of the study (the pre-intervention period) from August 1, 2008, until December 1, 2008, the patients’ data were collected related to SUP and physician prescribing of AST. Then an internal guideline for SUP, based on the ASHP protocol, was prepared by a clinical pharmacist in the infectious disease ward. After institutional approval, the team of clinical pharmacists (the authors) advised the physicians in charge for every patient on prescribing AST for SUP in situations when there was an indication or advised the discontinuation of AST when not warranted by patient risk factors. These recommendations were based on the prepared form that was used for risk assessments of hospitalized patients (Figure 1). If the patient had at least 1 primary (“absolute”) risk factor or 2 or more secondary (“relative”) risk factors, the clinical pharmacist recommended the use of AST. Also, the importance of implementing the SUP guideline was emphasized for the attending physicians in a group meeting before the post-intervention period of the study. The patient’s physician approved or rejected the clinical pharmacist recommendations for the proper use of AST for SUP based on his or her own clinical judgment. The post-intervention phase of the study was the 4-month period from February 1, 2009, to June 1, 2009.

SUP has been defined as the prescription of histamine2-receptor antagonists [H2RAs], PPIs, antacids, misoprostol, or sucralfate. Although antacids are effective in preventing SUP, their use has declined due to frequent and difficult administration regimens with the continuous need of intragastric pH monitoring for dose titration, and their potential side effects. Prior to the introduction of PPIs, H2RAs were considered to be first-line agents in SUP. The superiority of PPIs versus H2RAs for SUP is uncertain, and institution-specific guidelines are recommended with preferred AST determined on the basis of drug cost.

At Imam Khomeini Hospital, only ranitidine and omeprazole are approved by the pharmacy and therapeutics committee for
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Internal Guideline for Gastric Ulcer Risk Assessment in Patients on the Infectious Disease Ward of Imam Khomeini Hospital

Absolute indications: conditions in which prophylaxis must be given (mandatory)

- Mechanical ventilation >48 hours
- Coagulopathy: Platelet < 50000 or INR > 1.5 or PTT > 2 times normal value
- History of gastrointestinal bleeding or peptic ulcer disease within 1 year

Relative indications: conditions in which prophylaxis could be given (optional)

- Sepsis
- Renal insufficiency
- Hepatic impairment
- Enteral feeding
- Glucocorticoids ( >250 mg per day hydrocortisone or equivalent)
- Unfractionated or low molecular weight heparin
- Warfarin
- History of NSAID use >3 month
- An ICU stay of more than 1 week
- Occult bleeding lasting 6 days or more

*This guideline was adopted in January 2009.

ICU = intensive care unit; INR = international normalized ratio; mg = milligrams; NSAID = nonsteroidal anti-inflammatory drug; PTT = partial thromboplastin time.

AST. This hospital operates under significant budget constraints, and there are only a limited number of medications on the hospital formulary. Also, PPIs other than omeprazole are not covered by government insurance.

All patients for whom AST was given for a specific indication or appropriate treatment purpose were not counted as having received SUP (e.g., patients on AST for gastroesophageal reflux disease [GERD], peptic ulcer disease [PUD], dyspepsia, recent acute or suspected gastrointestinal [GI] bleeding) and were excluded (4 patients in both pre- and post-intervention periods).

For each patient, the admitting diagnoses and the type and number of antisecretory medications used for SUP were recorded.

Appropriate administration of SUP was defined by the internal guideline that was based on the ASHP guidelines (Figure 1); therefore, prophylaxis was recommended in patients:

- with coagulopathy (defined as platelet count < 50000 cubic millimeters [mm$^3$] or an International Normalized Ratio [INR] of >1.5, or a partial thromboplastin time > 2 times the control value)
- requiring mechanical ventilation for more than 48 hours
- with a history of GI ulceration or bleeding within 1 year before admission
- with at least 2 of the following risk factors: sepsis, ICU stay of more than 1 week, occult bleeding lasting 6 days or more, use of high-dose corticosteroids (> 250 milligrams [mg] per day of hydrocortisone or the equivalent), recent use of nonsteroidal anti-inflammatory drugs (NSAIDs) for more than 3 months, renal or liver failure, and anticoagulant use.

For patients in whom only 1 of the mentioned risk factors was present, indicating a relative indication for AST, the physician would decide whether to administer AST.

All of the patients in both study periods were assessed for indications for receipt of SUP, whether AST was received, and whether AST was continued upon discharge.

Statistical analyses were performed using SPSS version 11. The Pearson chi-square test was used for statistical analysis of data, comparing the pre- and post-intervention periods. The a priori statistical significance level was 0.05.

Results

In the pre-intervention period, 269 patients were evaluated, and 262 (54% men and 46% women; Table 1) were included in the study after exclusion of 7 patients (3 patients expired before the completion of the study, and 4 patients received AST before admission; Figure 2). In the post-intervention period after the implementation of the internal guideline for SUP, there were 245 patients admitted to the infectious disease ward. Of these, 240 patients (51% men and 49% women) were included in the study (Table 1) after exclusion of 5 patients (1 patient expired before the completion of the study, and 4 patients were on AST before admission; Figure 2). About one-third of the patients in both the pre- and post-intervention periods had pre-existing conditions of either human immunodeficiency virus (HIV) or tuberculosis (Table 1).

Of the 3 risk factors that were considered to be absolute indications for the use of AST for SUP, there were no patients in either evaluation period of this study who had an indication for mechanical ventilation of more than 48 hours or who had GI ulceration or bleeding within 1 year prior to hospital admission (Table 2). Coagulopathy was the only indication for SUP in the entire study period, and 23 patients (8.8%) had this indication in the pre-intervention period versus 14 patients (5.8%) in the
post-intervention period.

For the lists of factors considered to be possible (“relative”) risk factors for SUP, the most common was use of heparin (19.5% of patients in the pre-intervention period and 14.6% of patients in the post-intervention period). Other common relative risk factors were NSAID use for more than 3 months (10.7% and 7.1% pre-intervention and post-intervention, respectively) and corticosteroid use (6.1% and 2.9% pre-intervention and post-intervention, respectively; Table 2). There were no patients who had 2 relative risk factors in either the pre-intervention or post-intervention study periods.

Of the 262 patients in the pre-intervention period, 80.9% (n=212) received AST compared with 113 of 240 patients (47.1%) in the post-intervention period (P<0.001; Table 3). Of the 23 patients in the pre-intervention period with an indication for SUP according to the internal ASHP-based guideline, 78.3% (n=18) received AST versus 85.7% (n=12 of 14) in the post-intervention period (P=0.575). Of the 239 patients without an indication for SUP, 194 (81.2%) received AST in the pre-intervention period versus 101 of 226 (44.7%) in the post-intervention period (P<0.001). Of the 212 patients who received AST in the pre-intervention period, 194 (91.5%) did not have an indication for SUP versus 101 of 113 (89.4%) in the post-intervention period (89.4%; P=0.528).

The administration of AST was not continued upon discharge in more than 95% of the patients in the pre- and post-intervention phases of the study. Omeprazole and ranitidine use rates for AST were nearly equal in the pre-intervention period (52% omeprazole and 48% ranitidine) with slightly higher omeprazole use in the post-intervention period (57% omeprazole and 43% ranitidine).

Discussion

In recent years, the use of AST in general medicine wards has become increasingly common despite the absence of evidence to support the need for SUP in the non-ICU setting.17 In one study of SUP in a general medical nursing unit (i.e., non-ICU patients) of a teaching hospital, Nardino et al. (2000) found that 54% of general medicine patients received AST, but 65% of patients were judged not to have an indication for SUP.2 Grube and May (2007) found in a literature review that inappropriate use of AST for SUP in general medicine wards was as high as 71%, and these authors concluded that (a) SUP in hospitalized general medicine patients is not recommended and (b) AST in these patients is not evidence-based.17

In the pre-intervention period of the present study, only 8.8% of patients in the infectious disease ward had an indication for SUP but 80.9% received AST for SUP. In the post-intervention period, only 14 of 240 patients (5.8%) had an indication for SUP, but 113 patients (47.1%) received AST. This overuse contributes to patient exposure to avoidable drug cost and adverse events.

Prevalent use of SUP by physicians may be related to the perception that the side effects of PPIs and H2RAs are infrequent, especially when considering the short administration period and the relatively low cost of these medications.3 However, the side effects are not insignificant. More than 15 years ago, Cook et al. (1994) determined that the risk of clinically important bleeding was low in even critically ill patients, eliminating the need for SUP with AST in all but patients with either coagulopathy or who required medical ventilation.3

There has been some controversy regarding the medication of choice for AST in patients who meet the criteria for SUP. Results of a study by Estrad et al. (1999) showed that 77% of patients received H2RAs as the agent of choice,15 but this study was conducted prior to the explosive rise in use of PPIs. In contrast, the study by Pham et al. (2007) reported that PPIs accounted for 84%, H2RAs 11%, and combination therapy was used as prophylaxis in 5% of cases.11 Other studies also have reported that PPIs were the most frequently used AST for SUP.16,17 Omeprazole and ranitidine were the only 2 AST agents available at Imam Khomeini Hospital during the period of the present study and were used in nearly equal proportions in the pre-intervention period and a slightly higher proportion of omeprazole in the post-intervention period. The initial ASHP guidelines (1999) recommended that the selection of an AST agent of choice for SUP should be made by each institution based on analysis of the side effects and actual

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**Table 1** Patient Characteristics Including Pre-Existing Conditions

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pre-Intervention n (%)</th>
<th>Post-Intervention n (%)</th>
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<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>141 (53.8)</td>
<td>122 (50.8)</td>
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<tr>
<td>Female</td>
<td>121 (46.2)</td>
<td>118 (49.2)</td>
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<tr>
<td>Age group (years)</td>
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<tr>
<td>10-19</td>
<td>18 (6.9)</td>
<td>25 (10.4)</td>
</tr>
<tr>
<td>20-39</td>
<td>114 (43.5)</td>
<td>104 (43.3)</td>
</tr>
<tr>
<td>40-59</td>
<td>71 (27.1)</td>
<td>63 (26.3)</td>
</tr>
<tr>
<td>60-79</td>
<td>44 (16.8)</td>
<td>37 (15.4)</td>
</tr>
<tr>
<td>80 or older</td>
<td>15 (5.7)</td>
<td>11 (4.6)</td>
</tr>
<tr>
<td>Pre-existing disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>54 (20.6)</td>
<td>47 (19.6)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>34 (13.0)</td>
<td>30 (12.5)</td>
</tr>
<tr>
<td>Diabetic foot</td>
<td>24 (9.2)</td>
<td>21 (8.8)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>15 (5.7)</td>
<td>20 (8.3)</td>
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<tr>
<td>Pneumonia</td>
<td>18 (6.9)</td>
<td>16 (6.7)</td>
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<tr>
<td>Osteomyelitis</td>
<td>18 (6.9)</td>
<td>16 (6.7)</td>
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<td>Brucellosis</td>
<td>16 (6.1)</td>
<td>15 (6.3)</td>
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<tr>
<td>Endocarditis</td>
<td>12 (4.6)</td>
<td>13 (5.4)</td>
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<tr>
<td>Pyelonephritis</td>
<td>11 (4.2)</td>
<td>10 (4.2)</td>
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<tr>
<td>Meningitis</td>
<td>12 (4.6)</td>
<td>10 (4.2)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>11 (4.2)</td>
<td>10 (4.2)</td>
</tr>
<tr>
<td>Abscess</td>
<td>11 (4.2)</td>
<td>9 (3.8)</td>
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<tr>
<td>Bed sore</td>
<td>9 (3.4)</td>
<td>7 (2.9)</td>
</tr>
<tr>
<td>FUO</td>
<td>9 (3.4)</td>
<td>7 (2.9)</td>
</tr>
<tr>
<td>Necrotizing fascitis</td>
<td>4 (1.5)</td>
<td>5 (2.1)</td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>4 (1.5)</td>
<td>4 (1.7)</td>
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*Pre-existing was defined as a problem or disease that the patient had at the time of admission.

AIDS = acquired immune deficiency syndrome; FUO = fever of unknown origin; HIV = human immunodeficiency virus.
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The update by Allen et al. (2004) reinforced the point that the AST agent of choice should be based primarily on actual cost because there was not sufficient evidence of a difference in efficacy for SUP. Although there appears to be no evidence of superiority of PPIs over H2RAs in SUP, PPIs have become the most commonly used medications for SUP. Post-discharge use of AST in general, and PPIs in particular, can add cost for patients without benefit, and pharmacy interventions such as stop orders, restriction of the use of PPIs for SUP in non-ICU settings, and “meticulous chart review to ensure that hospitalized patients are not discharged home on a PPI without an appropriate indication” might be used to reduce waste from overuse after hospital discharge.

Despite the relative safety of PPIs and H2RAs, SUP is not warranted in patients at low risk for clinically important bleeding (e.g., patients not receiving mechanical ventilation and those without significant coagulopathy). Generally, it is not cost-effective to use AST to prevent GI bleeding except in the

FIGURE 2 Patient Selection Flow Chart

Pre-intervention period
August 1, 2008 – December 1, 2008

Patients admitted to the infectious disease ward (n=269)

Total number of patients included in the study (n=265)

Patient data available for analysis (n=262)

Excluded (n=4): Patients who were on acid-suppressive therapy before admission

Lost to follow up: Died during hospitalization due to a cause other than gastrointestinal disorders (n=3)

Post-intervention period
February 1, 2009 – June 1, 2009

Patients admitted to the infectious disease ward (n=245)

Total number of patients included in the study (n=241)

Patient data available for analysis (n=240)

Excluded (n=4): Patients who were on acid-suppressive therapy before admission

Lost to follow up: Died during hospitalization due to a cause other than gastrointestinal disorders (n=1)
highest-risk patients. In the present study, 91.5% of patients in the pre-intervention period who received AST had no indication for SUP, and 89.4% of patients who received AST in the post-intervention period had no indication for SUP.

Unnecessary use of AST is wasteful, and Herzig et al. (2009) found that acid-suppressive medication use resulted in a 30% increase in the odds of hospital-acquired pneumonia. In subgroup analysis, the incidence of hospital-acquired pneumonia was 5.3% for PPIs (adjusted odds ratio OR = 1.3, 95% confidence interval CI = 1.1-1.4) and 3.1% for H2RAs (OR = 1.2, 95% CI = 0.98-1.4), with the increased risk statistically significant for PPIs, which accounted for 82% of the AST use. Inappropriate SUP also imposes unnecessary direct drug cost on health systems. In a retrospective study by Heidelberg and Inadomi (2006) on adult non-ICU admissions to 1 family medicine and 5 general internal medicine teaching services over a consecutive 4-month period, 22.1% of patients were receiving AST for SUP without an indication as defined by the ASHP guidelines. The inpatient cost of inappropriate stress ulcer prophylaxis was $11,024 over 4 months or an annualized direct drug cost of $44,096.

Coursol and Sanzari (2005) found that a SUP algorithm implemented by pharmacists in the ICU of Royal Victoria Hospital was associated with reduction in use of inappropriate SUP including the number of days of inappropriate prophylaxis and AST drug cost (intravenous famotidine or omeprazole suspension or tablets) per patient. Other researchers have reported effects of interventions with SUP guidelines including Mostafa et al. (2002), who reported results similar to the findings of this study—overall reduction in use of AST, reduction in inappropriate use of AST, but no change in appropriate use of AST for SUP in the ICU setting. Pitimana-aree et al. (1998) reported increased appropriate use of SUP and reduced drug cost for AST after implementation of a SUP guideline in the ICU setting.

It has been suggested that the incidence of hospital-acquired GI bleeding in noncritically ill medical patients is low, but treatment with anticoagulants predisposes to this complication. Qadeer et al. (2006) found that the rate of nosocomial GI bleeding was low (0.4%) among 17,707 non-ICU general medicine inpatients over a 4-year period, and the only important risk factor for GI bleeding was full-dose anticoagulants or clopidogrel.

In the present study, there were 5 patients in the pre-intervention period and 2 patients in the post-intervention period who met the criteria for AST due to coagulopathy but did not receive either omeprazole or ranitidine. We are uncertain why these patients did not receive AST per the internal SUP guideline, but contributing factors probably include individual physician judgment to not follow the guideline or physician ignorance of the existence of the guideline. This outcome caused the clinical pharmacy staff to have periodic meetings with medical residents regarding all ongoing clinical care.

Limitations

The definition of stress-induced bleeding is highly variable and depends on the definition of bleeding. Definition of clinically important stress-related GI bleeding in the hospital environment...
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Study concept and design were contributed primarily by Khalili and Tabeefar. Data collection was performed primarily by Haj Hossein Talasaz and Hendoee. The data were interpreted primarily by Khalili and Dashi-Khavikidi. The manuscript was written primarily by Khalili, Haj Hossein Talasaz, and Hendoee and revised primarily by Khalili and Haj Hossein Talasaz.

REFERENCES

includes a significant drop in hemoglobin (greater than 2 grams per deciliter [gm per dL]) and positive endoscopic findings.25,28 The foremost limitation of the present study was failure to assess clinical outcomes, including actual occurrence of GI bleeding. Therefore, it is not possible to determine if SUP or withholding AST was associated with GI bleeding. Second, the use of AST for SUP in the non-ICU setting is controversial and not supported by the available evidence.27 However, we were interested in studying the influence of the SUP practice guideline and clinical pharmacist intervention on the use of AST in general as well as evidence-based appropriate use. Third, the influence of our intervention may have been reduced by turnover of physicians in the infectious disease ward of this hospital because the study site is a teaching hospital with rotation of physicians among wards of the hospital.

Conclusion
Introduction by pharmacists of a treatment guideline for SUP in the infectious disease ward of Imam Khomeini Hospital was associated with a reduction in overall use of AST and a reduction in use of AST for patients without an indication for SUP. However, there was no significant change in the appropriate use of AST in patients with an indication for SUP.

| TABLE 3 | Absolute Indications for SUP and Receipt of AST Prophylaxis |
|-----------------|-----------------|-----------------|
| **Pre-intervention** | **Indication for SUP** | **Total** |
| Prophylaxis with omeprazole or ranitidine | Yes | No | Patients Who Received AST Without an Indication for SUP |
| Yes | 18 (78.3%) | 194 (81.2%) | 212 (80.9%) | 91.5% (194 of 212) |
| No | 5 (21.7%) | 45 (18.8%) | 50 (19.1%) | |
| Totals | 23 (100.0%) | 239 (100.0%) | 262 (100.0%) | |

| **Post-intervention** | **Indication for SUP** | **Total** |
| Prophylaxis with omeprazole or ranitidine | Yes | No | Patients Who Received AST Without an Indication for SUP |
| Yes | 12 (85.7%) | 101 (44.7%) | 113 (47.1%) | 89.4% (101 of 113) |
| No | 2 (14.3%) | 125 (55.3%) | 127 (52.9%) | |
| Totals | 14 (100.0%) | 226 (100.0%) | 240 (100.0%) | |

*From Table 2.*

**P = 0.575 for the Pearson chi-square comparison.**

**P < 0.001 for the Pearson chi-square comparison.**

**P = 0.001 for the Pearson chi-square comparison.**

**P = 0.528 for the Pearson chi-square comparison.**

AST = acid-suppressive therapy; SUP = stress ulcer prophylaxis.
Descriptive Analysis of a Clinical Pharmacy Intervention to Improve the Appropriate Use of Stress Ulcer Prophylaxis in a Hospital Infectious Disease Ward


