PRACTICE MANAGEMENT GUIDELINES FOR STRESS ULCER PROPHYLAXIS

EAST Practice Management Guidelines Committee

Oscar D. Guillamondegui, MD; Oliver L. Gunter, Jr., MD; John A. Bonadies, MD; Jay E. Coates, DO; Stanley J. Kurek, DO; Marc A. De Moya, MD; Ronald F. Sing, DO; Alan J. Sori MD

Chairman

Oscar D. Guillamondegui, M.D.

Vanderbilt University Medical Center

Nashville, Tennessee

oscar.guillamondegui@vanderbilt.edu

Vice-Chair

Oliver L. Gunter Jr., M.D.

Washington University, St. Louis

St. Louis, Missouri

guntero@wudosis.wustl.edu

Committee members

John A. Bonadies, M.D.

Hospital of Saint Raphael

New Haven, Connecticut

Jay E. Coates, D.O.

University of Nevada, Las Vegas

Las Vegas, Nevada

Stanley J. Kurek, D.O.

University of Tennessee

Knoxville, Tennessee

Marc A. De Moya, M.D.

Massachusetts General Hospital

Boston, Massachusetts

Ronald F. Sing, D.O.

Carolinas Medical Center

Charlotte, North Carolina

Alan J. Sori, M.D.

St. Joseph Medical Center

Patterson, New Jersey

Statement of the Problem

Stress ulcer prophylaxis has historically been a disease process with a high degree of prevalence in the setting of burns and trauma. Multiple protocols exist for prophylaxis of stress ulcer, but there are no universally accepted regiments. This has led to nationwide disorganization in current practice a stress ulcer prophylaxis. There also remains no universal determination of need for stress ulcer prophylaxis in the trauma population.

The development of clinically significant gastrointestinal hemorrhage has been associated with significant increase of morbidity and mortality. Increase of mortality may be increased as high as 50%.

Process

A MEDLINE search was performed from the years 1990 to present with the following subject words: Gastrointestinal prophylaxis, gastrointestinal hemorrhage, intensive care unit, stress ulcer prophylaxis, trauma, and critical care. All articles pertaining to the critically ill patient were reviewed by 8 trauma intensivists for adequacy and pertinence to the subject.

Quality of the references

The initial literature review identified 119 articles. Of these, 73 were removed secondary to inadequate or inappropriate data. A table of evidence was constructed using the 46 references that were identified. *See table 1.* (1-46)

The article was entered into a review data sheet that summarized the main conclusions of the study and identified any deficiencies. Reviewers classified each references Class I, Class II or Class III data.

The references were classified using methodology established by the Agency for Health Care Policy and Research (AHCPR) of the U. S. Department of Health and Human Services. Additional criteria and specifications were used for Class I articles from a tool described by Oxman et al. (47)

Articles were categorized as Class I, Class II or Class III data according to the following definitions:

> **Class I**: A prospective randomized clinical trial.
>
> **Class II**: A prospective non-comparative clinical study or a retrospective analysis based on reliable data.
>
> **Class III**: A retrospective case series or database review.

The 46 references that met criteria were classified as follows: 27 Class I, 9 Class II, and 10 Class III.

Recommendations from the practice management guideline committee were made on the basis of studies that were included in the evidentiary table. The quality assessment instrument applied to references was that developed by the Brain Trauma Foundation and subsequently adopted by the EAST Practice Management Guidelines Committee. (48) Recommendations were categorized based on the class of data from which they were derived.

Recommendations

What are the risk factors for stress ulcer development and which patients require prophylaxis?

1. Level 1 recommendations
    i. Prophylaxis is recommended for all patients with:
        1. Mechanical ventilation
        2. Coagulopathy
        3. Traumatic brain injury
        4. Major burn injury
2. Level 2 recommendations
    i. Prophylaxis is recommended for all ICU patients with:
        1. Multi-trauma
        2. Sepsis

3. Acute renal failure

3. Level 3 recommendations
    i. Prophylaxis is recommended for all ICU patients with:
        1. ISS>15
        2. Requirement of high-dose steroids (>250 mg hydrocortisone or equivalent per day)
    ii. In selected populations, no prophylaxis is necessary

Is there a preferred agent for stress ulcer prophylaxis? If so, which?

1. Level 1 recommendations
    i. There is no difference between H_2 antagonists, cytoprotective agents, and some proton pump inhibitors
    ii. Antacids should not be used as stress ulcer prophylaxis.

2. Level 2 recommendations
    i. Aluminum containing compounds should not be used in patients on dialysis

3. Level 3 recommendations
    i. Enteral feeding alone may be insufficient stress ulcer prophylaxis

What is the duration of prophylaxis?

1. Level 1 recommendations
    i. There were no level 1 recommendations

2. Level 2 recommendations
    i. During mechanical ventilation or intensive care unit stay

3. Level 3 recommendations
    i. Until able to tolerate enteral nutrition

Scientific Foundation

Historical

Stress ulcer prophylaxis has been an important part of the care for critical illness for over 20 years. Maynard et al. demonstrated alterations in splanchnic blood flow during acute illness. (49) The physiology of critical illness is frequently complicated with multiple systemic inflammatory abnormalities as well as alterations in hemodynamic status. Systemic hypoperfusion with associated catecholamine search, decreased cardiac output, hypovolemia, vasoconstriction, and inflammatory cytokine release is associated with splanchnic hypoperfusion. In comparison to normal patients, critically ill patients may

have disturbances in their mucous and bicarbonate protective layer, owing to alterations in mucosal microcirculation. (26)

Overall, the rate of clinically important upper gastrointestinal hemorrhage is low, and is currently rarely seen as a complication of critical illness owing to several potential factors, including strict regimens of prophylaxis. Clinical importance has classically been described as obvious physiologic decline, the requirement of operative for endoscopic intervention, and transfusion requirement. Use of protective agents has historically led to at least a 50% decrease in clinically significant hemorrhage. (50)

Risk Factors

Multiple studies have identified a myriad of risk factors for the development of stress ulceration, although this has not been studied in recent years. Based on the current literature review, the most universally accepted risk factors for stress ulceration are prolonged mechanical ventilation and coagulopathy. (4, 22, 28, 30, 38) Other identified risk factors include multiple injuries, spinal cord injury, injury severity score greater than 15, acute renal failure, and requirement of high-dose steroids. (3, 6, 16, 26, 33, 34)

Timing and duration

If stress ulcer prophylaxis is to be initiated, it should be done so at the onset of risk factors. Based on the current literature review, it is unclear when prophylaxis should be discontinued. Although it has been recommended that prophylaxis be continued for at

least 7 days, this has failed to show a difference in outcomes of mortality or GI bleeding. Most studies recommend the continuation of stress ulcer prophylaxis throughout the duration of critical illness or intensive care unit stay. (29, 38, 41) This strategy would be individualized based on patient physiology. (27, 43)

Medication Choice

There are multiple pharmacologic options for the prophylaxis of stress ulceration.

Histamine-2 receptor antagonists

As a measure efficacy, gastric pH should be greater than 4. Tolerance to these medications has been seen, requiring increased dosing based upon gastric pH measurements. (51-53) Several studies have evaluated histamine receptor antagonists in comparison to cytoprotective agents, proton pump inhibitors, placebo, and various routes and dosages of administration with mixed results.

Proton pump inhibitors

All studies have shown them to be equivocal to histamine receptor antagonists. Tolerance has not been demonstrated to these medications, however. There currently are no large studies that prove superiority of proton pump inhibitors to histamine receptor antagonists for stress ulcer prophylaxis. (2, 54) Omeprazole suspension has been shown to be effective by any enteral route, and is superior to placebo in the prevention of stress ulceration. (34, 35)

Cytoprotective agents

Sucralfate has been the best studied and the most widely used agent in this category. Its use has not been associated with an increase in stress ulceration. Sucralfate has been shown to alter intraluminal pH levels which may affect the portion of further orally administered pharmacologic agents. (24, 46) Numerous studies have shown that the impact on gastric pH is less than that associated with histamine receptor antagonists or proton pump inhibitors which may impact gastric colonization. (4, 5, 8, 9, 14, 22, 27, 38, 43) One study showed increased potential of aluminum toxicity using sucralfate in patients with renal impairment. (55)

Antacids

Use of antacids has been associated with a potential increase in the risk of hemorrhage. These agents also have been implicated in an increase in mortality, and are currently not recommended for use. (43)

Enteral feeding

Currently, there is limited data supporting the use of enteral nutrition as the sole means of stress ulcer prophylaxis. There is controversy with regard to enteral nutrition administration in the setting of hemodynamic instability requiring pressor agents. Enteral feeding also has failed to show significant increases in gastric pH. There is controversy regarding protective effects of enteral nutrition and whether it is enough to warrant discontinuation of stress ulcer prophylaxis. (8, 19, 46)

No prophylaxis

There have been some retrospective studies that have evaluated the need for prophylaxis at all. These studies have been in a mixed ICU population primarily composed of medical patients, as opposed to trauma patients alone. (12, 17, 44, 45) Adequate prospective data is lacking to warrant recommending cessation of prophylaxis.

Summary

All critically ill patients with associated risk factors should receive chemical prophylaxis for stress ulceration. All agents (with the exception of antacids) appear equally adequate for prophylaxis against stress ulceration. The agent of choice should be based upon cost-effective arrangements between vendors and individual hospitals. The duration of treatment is ill-defined, but should be maintained while risk factors are present, the patient is admitted to the intensive care unit, or for a least one week after onset of critical illness. There is currently insufficient evidence to warrant cessation of prophylaxis in the setting of enteral nutrition if other risk factors exist, or to eliminate stress ulcer prophylaxis entirely.

References

1. Baghaie AA, Mojtahedzadeh M, Levine RL, et al. Comparison of the effect of intermittent administration and continuous infusion of famotidine on gastric pH in critically ill patients: results of a prospective, randomized, crossover study. *Crit Care Med* 1995;23:687-691.
2. Balaban DH, Duckworth CW, Peura DA. Nasogastric omeprazole: effects on gastric pH in critically Ill patients. *Am J Gastroenterol* 1997;92:79-83.
3. Ben-Menachem T, Fogel R, Patel RV, et al. Prophylaxis for stress-related gastric hemorrhage in the medical intensive care unit. A randomized, controlled, single-blind study. *Ann Intern Med* 1994;121:568-575.
4. Bonten MJ, Gaillard CA, van der Geest S, et al. The role of intragastric acidity and stress ulcus prophylaxis on colonization and infection in mechanically ventilated ICU patients. A stratified, randomized, double-blind study of sucralfate versus antacids. *Am J Respir Crit Care Med* 1995;152:1825-1834.
5. Bonten MJ, Gaillard CA, van Tiel FH, et al. Continuous enteral feeding counteracts preventive measures for gastric colonization in intensive care unit patients. *Crit Care Med* 1994;22:939-944.
6. Burgess P, Larson GM, Davidson P, et al. Effect of ranitidine on intragastric pH and stress-related upper gastrointestinal bleeding in patients with severe head injury. *Dig Dis Sci* 1995;40:645-650.
7. Conrad SA, Gabrielli A, Margolis B, et al. Randomized, double-blind comparison of immediate-release omeprazole oral suspension versus intravenous cimetidine

for the prevention of upper gastrointestinal bleeding in critically ill patients. *Crit Care Med* 2005;33:760-765.

8. Cook D, Heyland D, Griffith L, et al. Risk factors for clinically important upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. *Crit Care Med* 1999;27:2812-2817.

9. Cook D, Walter S, Freitag A, et al. Adjudicating ventilator-associated pneumonia in a randomized trial of critically ill patients. *J Crit Care* 1998;13:159-163.

10. Cook DJ, Fuller HD, Guyatt GH, et al. Risk factors for gastrointestinal bleeding in critically ill patients. Canadian Critical Care Trials Group. *N Engl J Med* 1994;330:377-381.

11. Cook DJ, Griffith LE, Walter SD, et al. The attributable mortality and length of intensive care unit stay of clinically important gastrointestinal bleeding in critically ill patients. *Crit Care* 2001;5:368-375.

12. Devlin JW, Ben-Menachem T, Ulep SK, et al. Stress ulcer prophylaxis in medical ICU patients: annual utilization in relation to the incidence of endoscopically proven stress ulceration. *Ann Pharmacother* 1998;32:869-874.

13. Eddleston JM, Pearson RC, Holland J, et al. Prospective endoscopic study of stress erosions and ulcers in critically ill adult patients treated with either sucralfate or placebo. *Crit Care Med* 1994;22:1949-1954.

14. Eddleston JM, Vohra A, Scott P, et al. A comparison of the frequency of stress ulceration and secondary pneumonia in sucralfate- or ranitidine-treated intensive care unit patients. *Crit Care Med* 1991;19:1491-1496.

15. Ephgrave KS, Kleiman-Wexler R, Pfaller M, et al. Effects of sucralfate vs antacids on gastric pathogens: results of a double-blind clinical trial. *Arch Surg* 1998;133:251-257.

16. Fabian TC, Boucher BA, Croce MA, et al. Pneumonia and stress ulceration in severely injured patients. A prospective evaluation of the effects of stress ulcer prophylaxis. *Arch Surg* 1993;128:185-191; discussion 191-182.

17. Faisy C, Guerot E, Diehl JL, et al. Clinically significant gastrointestinal bleeding in critically ill patients with and without stress-ulcer prophylaxis. *Intensive Care Med* 2003;29:1306-1313.

18. Geus WP, Vinks AA, Smith SJ, et al. Comparison of two intravenous ranitidine regimens in a homogeneous population of intensive care unit patients. *Aliment Pharmacol Ther* 1993;7:451-457.

19. Gurman G, Samri M, Sarov B, et al. The rate of gastrointestinal bleeding in a general ICU population: a retrospective study. *Intensive Care Med* 1990;16:44-49.

20. Hanisch EW, Encke A, Naujoks F, et al. A randomized, double-blind trial for stress ulcer prophylaxis shows no evidence of increased pneumonia. *Am J Surg* 1998;176:453-457.

21. Heiselman DE, Hulisz DT, Fricker R, et al. Randomized comparison of gastric pH control with intermittent and continuous intravenous infusion of famotidine in ICU patients. *Am J Gastroenterol* 1995;90:277-279.

22. Kantorova I, Svoboda P, Scheer P, et al. Stress ulcer prophylaxis in critically ill patients: a randomized controlled trial. *Hepatogastroenterology* 2004;51:757-761.

23. Kitler ME, Hays A, Enterline JP, et al. Preventing postoperative acute bleeding of the upper part of the gastrointestinal tract. *Surg Gynecol Obstet* 1990;171:366-372.

24. Lasky MR, Metzler MH, Phillips JO. A prospective study of omeprazole suspension to prevent clinically significant gastrointestinal bleeding from stress ulcers in mechanically ventilated trauma patients. *J Trauma* 1998;44:527-533.

25. Laterre PF, Horsmans Y. Intravenous omeprazole in critically ill patients: a randomized, crossover study comparing 40 with 80 mg plus 8 mg/hour on intragastric pH. *Crit Care Med* 2001;29:1931-1935.

26. Levy MJ, Seelig CB, Robinson NJ, et al. Comparison of omeprazole and ranitidine for stress ulcer prophylaxis. *Dig Dis Sci* 1997;42:1255-1259.

27. Maier RV, Mitchell D, Gentilello L. Optimal therapy for stress gastritis. *Ann Surg* 1994;220:353-360; discussion 360-353.

28. Martin LF, Booth FV, Karlstadt RG, et al. Continuous intravenous cimetidine decreases stress-related upper gastrointestinal hemorrhage without promoting pneumonia. *Crit Care Med* 1993;21:19-30.

29. Martin LF, Booth FV, Reines HD, et al. Stress ulcers and organ failure in intubated patients in surgical intensive care units. *Ann Surg* 1992;215:332-337.

30. Metz CA, Livingston DH, Smith JS, et al. Impact of multiple risk factors and ranitidine prophylaxis on the development of stress-related upper gastrointestinal bleeding: a prospective, multicenter, double-blind, randomized trial. The Ranitidine Head Injury Study Group. *Crit Care Med* 1993;21:1844-1849.

31. Mulla H, Peek G, Upton D, et al. Plasma aluminum levels during sucralfate prophylaxis for stress ulceration in critically ill patients on continuous venovenous hemofiltration: a randomized, controlled trial. *Crit Care Med* 2001;29:267-271.

32. Mustafa NA, Akturk G, Ozen I, et al. Acute stress bleeding prophylaxis with sucralfate versus ranitidine and incidence of secondary pneumonia in intensive care unit patients. *Intensive Care Med* 1995;21:287.

33. Pemberton LB, Schaefer N, Goehring L, et al. Oral ranitidine as prophylaxis for gastric stress ulcers in intensive care unit patients: serum concentrations and cost comparisons. *Crit Care Med* 1993;21:339-342.

34. Phillips JO, Metzler MH, Palmieri MT, et al. A prospective study of simplified omeprazole suspension for the prophylaxis of stress-related mucosal damage. *Crit Care Med* 1996;24:1793-1800.

35. Phillips JO, Olsen KM, Rebuck JA, et al. A randomized, pharmacokinetic and pharmacodynamic, cross-over study of duodenal or jejunal administration compared to nasogastric administration of omeprazole suspension in patients at risk for stress ulcers. *Am J Gastroenterol* 2001;96:367-372.

36. Pickworth KK, Falcone RE, Hoogeboom JE, et al. Occurrence of nosocomial pneumonia in mechanically ventilated trauma patients: a comparison of sucralfate and ranitidine. *Crit Care Med* 1993;21:1856-1862.

37. Pimentel M, Roberts DE, Bernstein CN, et al. Clinically significant gastrointestinal bleeding in critically ill patients in an era of prophylaxis. *Am J Gastroenterol* 2000;95:2801-2806.

38. Prod'hom G, Leuenberger P, Koerfer J, et al. Nosocomial pneumonia in mechanically ventilated patients receiving antacid, ranitidine, or sucralfate as prophylaxis for stress ulcer. A randomized controlled trial. *Ann Intern Med* 1994;120:653-662.

39. Ruiz-Santana S, Ortiz E, Gonzalez B, et al. Stress-induced gastroduodenal lesions and total parenteral nutrition in critically ill patients: frequency, complications, and the value of prophylactic treatment. A prospective, randomized study. *Crit Care Med* 1991;19:887-891.

40. Ryan P, Dawson J, Teres D, et al. Nosocomial pneumonia during stress ulcer prophylaxis with cimetidine and sucralfate. *Arch Surg* 1993;128:1353-1357.

41. Simms HH, DeMaria E, McDonald L, et al. Role of gastric colonization in the development of pneumonia in critically ill trauma patients: results of a prospective randomized trial. *J Trauma* 1991;31:531-536; discussion 536-537.

42. Simons RK, Hoyt DB, Winchell RJ, et al. A risk analysis of stress ulceration after trauma. *J Trauma* 1995;39:289-293; discussion 293-284.

43. Thomason MH, Payseur ES, Hakenewerth AM, et al. Nosocomial pneumonia in ventilated trauma patients during stress ulcer prophylaxis with sucralfate, antacid, and ranitidine. *J Trauma* 1996;41:503-508.

44. Zandstra DF, Stoutenbeek CP. The virtual absence of stress-ulceration related bleeding in ICU patients receiving prolonged mechanical ventilation without any prophylaxis. A prospective cohort study. *Intensive Care Med* 1994;20:335-340.

45. Zeltsman D, Rowland M, Shanavas Z, et al. Is the incidence of hemorrhagic stress ulceration in surgical critically ill patients affected by modern antacid prophylaxis? *Am Surg* 1996;62:1010-1013.

46. Devlin JW, Claire KS, Dulchavsky SA, et al. Impact of trauma stress ulcer prophylaxis guidelines on drug cost and frequency of major gastrointestinal bleeding. *Pharmacotherapy* 1999;19:452-460.

47. Oxman AD. Checklists for review articles. *BMJ* 1994;309:648-651.

48. Eastern Association for the Surgery of Trauma, EAST Ad Hoc Committee on Practice Management Guideline

Development.

49. Maynard N, Bihari D, Beale R, et al. Assessment of splanchnic oxygenation by gastric tonometry in patients with acute circulatory failure. *JAMA* 1993;270:1203-1210.

50. Cook DJ, Reeve BK, Guyatt GH, et al. Stress ulcer prophylaxis in critically ill patients. Resolving discordant meta-analyses. *JAMA* 1996;275:308-314.

51. Merki HS, Wilder-Smith CH. Do continuous infusions of omeprazole and ranitidine retain their effect with prolonged dosing? *Gastroenterology* 1994;106:60-64.

52. Netzer P, Gut A, Heer R, et al. Five-year audit of ambulatory 24-hour esophageal pH-manometry in clinical practice. *Scand J Gastroenterol* 1999;34:676-682.

53. Wilson P, Clark GW, Anselmino M, et al. Comparison of an intravenous bolus of famotidine and Mylanta II for the control of gastric pH in critically ill patients. *Am J Surg* 1993;166:621-624; discussion 624-625.

54. Mallow S, Rebuck JA, Osler T, et al. Do proton pump inhibitors increase the incidence of nosocomial pneumonia and related infectious complications when compared with histamine-2 receptor antagonists in critically ill trauma patients? *Curr Surg* 2004;61:452-458.

55. Tryba M, Kurz-Muller K, Donner B. Plasma aluminum concentrations in long-term mechanically ventilated patients receiving stress ulcer prophylaxis with sucralfate. *Crit Care Med* 1994;22:1769-1773.

56. Allen ME, Kopp BJ, Erstad BL. Stress ulcer prophylaxis in the postoperative period. *Am J Health Syst Pharm* 2004;61:588-596.

57. Cash BD. Evidence-based medicine as it applies to acid suppression in the hospitalized patient. *Crit Care Med* 2002;30:S373-378.

58. Jung R, MacLaren R. Proton-pump inhibitors for stress ulcer prophylaxis in critically ill patients. *Ann Pharmacother* 2002;36:1929-1937.

Evidence Table EAST Stress Ulcer Prophylaxis Practice Management Guideline 2007

First author	Year	Reference title	Reference	Study Design	Class of data for article	What are the risk factors for stress ulcer development and which trauma patients require prophylaxis ?	Class of data for question	Is there a preferred agent for stress ulcer prophylaxis? If so, what?	Class of data for question	What is the appropriate duration for stress ulcer prophylaxis in this population?	Class of data for question	Comments
Baghaie AA	1995	Comparison of the effect of intermittent administration and continuous infusion of famotidine on gastric pH in critically ill patients: results of a prospective randomized crossover study.	Crit Care Med. 1995 Apr;23(4):687-91.	Prospective crossover study on 15 patients comparing gastric pH during continuous and bolus famotidine administration	2	Did not address this question		Did not address this question		Did not address this question		Continuous infusion is more effective than intermittent dosages in maintaining the "appropriate gastric pH" necessary for SUP
Balaban DH	1997	Nasogastric omeprazole: effects on gastric pH in critically ill patients.	Am J Gastroenterol. 1997 Jan;92(1):79-83.	Prospective, non-randomized on 10 medical ICU patients, looking at effects of omeprazole and ranitidine on gastric pH.	2	Did not address this question		Yes, omeprazole	2	Did not address this question		NGT omeprazole maintained an intragastric pH of > 4.0, and was cost-effective in comparison to ranitidine or famotidine.
Ben Menachem T	1994	Prophylaxis for stress-related gastric hemorrhage in the MICU	Ann Intern Med. 1994 Oct 15;121(8):568-75.	Prospective, randomized, single-blind trial on 300 patients in the MICU comparing placebo, oral sucralfate, or IV infusion of ranitidine.	1	Respiratory failure, shock, sepsis, cardiac arrest, liver failure, ARF, coagulopathy, pancreatitis, high-dose steroids, anticoagulation	2	No difference between cimetidine, sucralfate, and placebo	1			Medical patients only. Patients with GI bleed 3 RF vs no bleed 2 RF. There was no difference in GI bleed with prophylaxis, but ?underpowered.
Bonten MJ	1994	Continuous enteral feeding counteracts preventive measures for gastric colonization in ICU patients	Crit Care Med. 1994 Jun;22(6):939-44.	Prospective, non-randomized trial eval change in gastric pH with	2	Did not address this question		No	2	Did not address this question.		Sucralfate with topical ABX was equivalent to STD prophylaxis in prevention of gastric colonization unless pt received enteral feeding. pH was lower in sucralfate group. No mention of GIB outcomes.
Bonten MJ	1995	The role of intragastric acidity and stress ulcer prophylaxis on colonization and infection in mechanically ventilated ICU patients. A stratified, randomized double-blind study of sucralfate versus antacids.	Am J Respir Crit Care Med. 1995 Dec;152(6 Pt 1):1825-34.	Single center RCT comparing antacids vs sucralfate, 112 pts, stratified by gastric pH. Outcome measures: VAP, gastric pH, gastric colonization.	1	Mechanical ventilation	1	No difference between sucralfate and antacids	2	Did not address this question		VAP rates, mortality rates, and gastric colonization rates were all similar.
Burgess P	1995	Effect of ranitidine on intragastric pH and stress related upper gastrointestinal bleeding in patients with severe head injury	Dig Dis Sci. 1995 Mar;40(3):645-50.	Single center, RCT,34 patients with traumatic brain injury. Comparison: ranitidine infusion versus placebo. Outcome: GIB, gastric pH.	1	Severe TBI, mechanical ventilation, renal insufficiency, hepatic insufficiency, hypotension, surgery, multi-trauma.	2	Yes, ranitidine	1	3 days minimum	2	Small study that showed risk of bleeding significantly increased with decreased gastric pH. Ranitidine effectively increased gastric pH and reduced GIB.
Conrad SA	2005	Randomized, double-blind comparison of immediate-release omeprazole oral suspension versus intravenous cimetidine for the prevention of upper gastrointestinal bleeding in critically ill patients.	Crit Care Med. 2005 Apr;33(4):760-5.	RCT, multi-institutional, 359 pts. Comparison: oral omeprazole vs IV cimetidine. Outcome of GIB and change in gastric pH.	1	Did not address this question		Yes, omeprazole	1	Did not address this question.		Omeprazole (oral) superior to cimetidine (IV) at preventing any overt GIB, noninferior to cimetidine in prevention of clinically significant bleeding.
Cook D	1998	A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation.	N Engl J Med. 1998 Mar 19;338(12):7917.	Multicenter RCT 1200 pts. Comparison sucralfate with ranitidine. Outcome: GIB.	1	Did not address this question		Yes, ranitidine	1	Did not address this question.		Ranitidine superior to sucralfate in prevention of GIB in the ventilated ICU patients.
Cook D	1999	Risk factors for clinically important upper gastrointestinal bleeding in patients requiring mechanical ventilation.	Crit Care Med. 1999 Dec;27(12):2812-7.	Multicenter RCT, 1077 pts. Comparison: ranitidine IV vs sucralfate.	1	Thrombocytopenia, ARF, MOD, NPO	2	Ranitidine	1	Did not address this question		Ranitidine superior to sucralfate for GIB prevention. Enteral nutrition is protective.
Cook DJ	2001	The attributable mortality and length of ICU stay of clinically important gastrointestinal bleeding in critically ill patients.	Crit Care. 2001 Dec;5(6):368-75. Epub 2001 Oct 5.	Retrospective study MICU pts, outcome of ICU LOS and GIB	3	Mechanical ventilation	2	Did not address this question		Did not address this question		GIB increases mortality and ICU length of stay. Recommended selective prophylaxis.

Cook DJ	1994	Risk factors for gastrointestinal bleeding in critically ill patients.	N Engl J Med. 1994 Feb 10;330(6):377-81.	Retrospective study, single center, 2252 pts. Comparison: GIB vs no GIB.	2	Respiratory failure, shock, sepsis, cardiac arrest, liver failure, ARF, coagulopathy, pancreatitis, high-dose steroids, organ transplantation, anticoagulation	3	Did not address this question		When risk factors are no longer present	2	Most important risk factors or mechanical ventilation greater than 48 hours and coagulopathy. Prophylaxis decreases bleeding risk by 50%.
Devlin JW	1998	Stress ulcer prophylaxis in MICU patients: annual utilization in relation to the incidence of endoscopically proven stress ulceration.	Ann Pharmacother. 1998 Sep;32(9):869-74.	Retrospective study of MICU patients, single institution. Outcome of endoscopic GI stress ulceration.	3	Did not address this question		No prophylaxis is necessary	3	Did not address this question		MICU study showing that selective prophylaxis does not increase endoscopic GIB
Devlin JW	1999	Impact of trauma stress ulcer prophylaxis guidelines on drug cost and frequency of major gastrointestinal bleeding	Pharmacotherapy. 1999 Apr;19(4):452-60.	single center, retrospective, non-randomized, 300 patients. Comparison: Outcome: Cost, GIB. Pharmacy study.	3	TBI, SCI, coagulopathy, mech vent, postop with NGT, PUD last 6 mos, gastric tonometry, MD preference	3	Yes, cimetidine	3	Did not address this question		Discontinue after pt. tolerating a diet or enteral feeding. Gave cimetidine. Saved $5000 in 150 patients, and had no GI bleeding complications.
Eddleston J	1991	A comparison of frequency of stress ulceration and secondary pneumonia in sucralfate- or ranitidine-treated intensive care unit patients	Crit Care Med. 1991 Dec;19(12):1491-6.	Single center RCT, 60 patients. Comparison: sucralfate versus ranitidine. Outcome: stress ulceration, VAP, gastric pH.	1	SICU pts with mech vent and high risk for stress ulceration	2	Yes, sucralfate	1	Did not address this question		Gastric pH, colonization, and VAP increased with ranitidine, sucralfate recommended.
Eddleston JM	1994	Prospective endoscopic study of stress erosions and ulcers in critically ill adult patients treated with either sucralfate or placebo.	Crit Care Med. 1994 Dec;22(12):1949-54.	Prospective RCT, single institution. 26 pts, sucralfate vs placebo.	1	Did not address this question		Sucralfate	1	Did not address this question		Small study showing decrease endoscopic pathology with sucralfate.
Ephgrave KS	1998	Effects of sucralfate versus antacids on gastric pathogens: results of a double-blind clinical trial.	Arch Surg. 1998 Mar;133(3):2517.	Single center RCT comparing sucralfate vs antacids of 140 VA patients undergoing major surgery requiring NGT. Outcomes: gastric pH, pneumonia, GIB.	1	Did not address this question		No difference between sucralfate and antacids	1	Did not address this question		No difference in pneumonia or GIB between the study groups. Increased gastric colonization in antacids vs sucralfate, unclear significance.
Fabian, TC	1993	Pneumonia and stress ulceration in severely injured patients. A prospective evaluation of the effects of stress ulcer prophylaxis	Arch Surg. 1993 Feb;128(2):185-91; discussion 191-2.	Single center RCT, 278 trauma patients. Comparison: sucralfate, bolus cimetidine, infusion cimetidine. Outcome: Stress ulceration, pneumonia.	1	Spinal cord injury	2	No difference between cimetidine and sucralfate	2	Discontinued with discharge or death, minimum of 3 days.	2	No difference in VAP rates
Faisy C	2003	Clinically significant gastrointestinal bleeding in critically ill patients with and without stress-ulcer prophylaxis.	Intensive Care Med. 2003 Aug;29(8):1306-13. Epub 2003 Jun 26.	Single-center retrospective study, 1473 pts. Comparison: prophylaxis vs no prophylaxis.	3	Mechanical ventilation greater than 48 hours, coagulopathy and acute renal failure	3	No prophylaxis is necessary	3	Did not address this question		No difference in GIB with and without prophylaxis. Recommended further study.
Geus WP	1993	Comparison of two IV ranitidine regimens in a homogenous population of ICU patients.	Aliment Pharmacol Ther. 1993 Aug;7(4):451-7.	Single center RCT comparing infusion vs bolus ranitidine, 18 pts. Outcome measures: gastric pH	1	Did not address this question		Yes, ranitidine	3	Did not address this question		No difference between infusion vs bolus ranitidine.
Gurman G	1990	The rate of gastrointestinal bleeding in a general ICU population: a retrospective study.	Intensive Care Med. 1990;16(1):44-9.	Retrospective study 298 patients. Comparison b/w antacids, cimetidine, both, and enteral nutrition. Outcome: coffee-ground emesis or melena.	3	Did not address this question		Antacids +/- cimetidine	3	Continued until able to tolerate enteral nutrition	3	Stopped treatment with enteral feeding, no real data significance between antacid/H2 blocker patients, enteral feeding had increased hemorrhage
Hansich EW	1998	A randomized, double-blind trial for stress ulcer prophylaxis shows no evidence of increased pneumonia.	Am J Surg. 1998 Nov;176(5):453-7.	Single center, RCT, 158 patients. Comparison: placebo, ranitidine, pirenzepine. Outcome: VAP.	2	SICU and mechanically ventilated	2	No	2	Did not address this question		No difference between ranitidine and pirenzepine with regard to VAP. Placebo group had low incidence of GIB, ?powered to study this effect.
Heiselman DE	1995	Randomized comparison of gastric pH control with intermittent and continuous intravenous infusion of famotidine in ICU patients.	Am J Gastroenterol. 1995 Feb;90(2):277-9.	Singe center RCT, 40 patients. Comparison: continuous vs bolus famotidine. Outcome: gastric pH.	1	Did not address this question		Famotidine bolus followed by infusion	1	Did not address this question		No statistical difference in GI bleed, and hospital mortality. pH increased most in bolus followed by infusion.
Kantorova I	2004	Stress ulcer prophylaxis in critically ill patients: a randomized controlled trial.	Hepatogastroenterology. 2004 May-Jun;51(57):757-61.	Single center RCT, 287 patients. Comparison: omeprazole, famotidine, sucralfate, placebo. Outcome: GIB, pneumonia, gastric pH.	1	Coagulopathy	1	No	1	Did not address this question		No difference between any treatment arm and GIB, pneumonia. Increased gastric pH may increase pneumonia rate.
Kitler ME	1990	Preventing postoperative acute bleeding of the upper part of the gastrointestinal tract	Surg Gynecol Obstet. 1990 Nov;171(5):366-72.	Prospective randomized trial, 298 pts in the ICU comparing bioflavonoid, sucralfate, and Maalox.	1	Critically ill patients in the ICU, age >50 yrs.	2	No	1	Did not address this question		No difference in the bleeding based on the various treatments. Age >50 correlated to bleeding. Small study.

Lasky MR	1998	A prospective study of omeprazole suspension to prevent clinically significant gastrointestinal bleeding from stress ulcers in mechanically ventilated trauma patients.	J Trauma. 1998 Mar;44(3):527-33.	Single center, retrospective study, 60 pts. Comparison: None. Outcome: GIB, gastric pH, pneumonia.	3	Did not address this question		Yes, omeprazole	3	Did not address this question		Omeprazole suspension is safe and effective as prophylaxis. Gastric pH is appropriately elevated. Omeprazole suspension is cost-effective.
Laterre PF	2001	Intravenous omeprazole in critically ill patients: a crossover study comparing 40 with 80 mg plus 8 mg/hr on intragastric pH.	Crit Care Med. 2001 Oct;29(10):1931-5.	Single center prospective crossover trial, 10 pts. Comparison 40mg bolus omeprazole vs 80mg +8mg/hr gtt. Outcome: gastric pH.	2	Did not address this question		Yes, omeprazole 40 mg bolus /day	2	Did not address this question		40 mg PPI as good as higher doses and continuous infusion for gastric pH.
Levy MJ	1997	Comparison of omeprazole and ranitidine for stress ulcer prophylaxis	Dig Dis Sci. 1997 Jun;42(6):1255-9.	Prospective RCT, single institution, 67 pts. Comparison: ranitidine, omeprazole. Outcome: pneumonia, GIB.	1	Coagulopathy, burn, severe trauma, respiratory failure, coagulopathic, TBI, acute renal failure, sepsis	2	Yes, omeprazole	1	Did not address this question		Higher number of GIB in the ranitidine group in comparison to omeprazole, 11 vs 2. ?Underpowered secondary to low incidence. Unclear RE: risk factors. Duration not addressed.
Maier RV	1994	Optimal therapy for stress gastritis	Ann Surg. 1994 Sep;220(3):353-60; discussion 360-3.	Single center RCT in 98 trauma patients. Comparison: ranitidine +antacids vs sucralfate. Outcome: VAP, GIB, LOS, cost.	1	Did not address this question		No difference between sucralfate and ranitidine	1	Did not address this question		H2 blockers increase gastric pH more effectively, but no clinical difference in GIB episodes. pH and colonization may be responsible for pneumonia.
Martin LF	1993	Continuous intravenous cimetidine decreases stress-related upper gastrointestinal hemorrhage without promoting pneumonia.	Crit Care Med. 1993 Jan;21(1):19-30.	Multicenter RCT comparing IV cimetidine to placebo, 117 patients.	1	Major surgery, burns >30% TBSA, respiratory failure, multi-trauma, hypotensive, hypovolemic shock, metabolic acidosis, sepsis	1	Yes, cimetidine	1	Did not address this question		Good multicenter, double-blinded, placebo controlled study to compare continuous IV cimetidine to nothing. pH increases with H2 blockers, but not associated with increased rate of GIB
Martin LF	1992	Stress ulcers and organ failure in intubated patients in SICUs.	Ann Surg. 1992 Apr;215(4):332-7.	Multicenter RCT, 127 SICU patients. Comparison: PO misoprostol and IV placebo vs PO placebo and IV cimetidine. Outcome: GIB,	1	Mechanical ventilation in patients with hypotension or sepsis	2	No difference between misoprostol and cimetidine	1	14 days or ICU discharge	2	Aggressive endoscopic surveillance in very ill SICU population. Prophylaxis may not eliminate mucosal lesions, but does decrease surgically significant bleeding.
Metz CA	1993	Impact of multiple risk factors and ranitidine prophylaxis on the development of stress-related upper gastrointestinal bleeding: a prospective, multicenter, double-blind randomized trial.	Crit Care Med. 1993 Dec;21(12):1844-9.	Prospective, multicenter, RCT, ten ICUs. Comparison: infusion ranitidine vs placebo. Outcome GIB.	1	Head injury, mechanical ventilation, serum cr>20, SGOT or SGPT > twice normal, PLT<75K, PT>nl, SBP<90, major operation, other clinically important trauma (blunt chest/long bone fx), GCS<6, ASA use	1	Yes, ranitidine	1	Did not address this question		Good multicenter, double-blinded, placebo controlled study. Complications increased with 2 or more risk factors. Unclear definitions for UGIB.
Mulla H	2001	Plasma aluminum levels during sucralfate prophylaxis for stress ulceration in critically ill patients on continuous venovenous hemofiltration: a randomized, controlled trial.	Crit Care Med. 2001 Feb;29(2):267-71.	Single center RCT, 20 patients. Comparison: sucralfate versus IV ranitidine. Outcome: plasma aluminum samples.	1	Did not address this question		Should not use sucralfate in patients requiring CVVH	2	Did not address this question		Should not use sucralfate in patients undergoing CVVH
Mustafa NA	1995	Acute stress bleeding prophylaxis with sucralfate versus ranitidine and incidence of secondary pneumonia in ICU patients.	Intensive Care Med. 1995 Mar;21(3):287.	Single center RCT, 31 patients. Comparison: sucralfate versus ranitidine. Outcome: stress ulcer bleeding, pneumonia.	1	Did not address this question		no, sucralfate equivalent to ranitidine	2	Did not address this question		Small study, sucralfate comparable to ranitidine. Ranitidine increases gastric pH which may increase tracheobronchial colonization.
Pemberton LB	1993	Oral ranitidine as prophylaxis for gastric stress ulcers in intensive care unit patients: serum concentrations and cost comparisons.	Crit Care Med. 1993 Mar;21(3):339-42.	Single center prospective non-randomized trial, 18 patients. Comparison: ranitidine 150 mg versus 300 mg. Outcome: serum ranitidine concentrations.	2	Sepsis, mech vent, major trauma, hypotension (<90mmHg)	2	Yes, oral ranitidine	2	Did not address this question		Only looked at ranitidine, oral administration ok and lower dose (150mg)as effective as higher dose (300mg), given twice daily.
Phillips JO	1996	A prospective study of simplified omeprazole suspension for the prophylaxis of stress-related mucosal damage.	Crit Care Med. 1996 Nov;24(11):1793-800.	Prospective, unrandomized, single center study, mixed SICU population outcome with omeprazole suspension.	2	SICU patients with anticipated 48 hr stay and any one of the following: TBI, burns, ARF, acid-base d/o, multitrauma, coagulopathy, multiple operations, coma, hypotension >1hr, sepsis	2	Yes, omeprazole	3	Did not address this question		Shows efficacy and safety of PPI, no placebo group. Significant increase in pH.

Phillips JO	2001	A randomized, pharmacokinetic and pharmacodynamic, cross-over study of duodenal or jejunal administration compared to nasogastric administration of omeprazole suspension in patients at risk for stress ulcers.	Am J Gastroenterol. 2001 Feb;96(2):367-72.	Randomized cross-over study, 9 surgical patients. Comparison: gastric vs enteral route. Outcome: intragastric pH.	2	Mechanical ventilation	2	Did not address this question		Did not address this question		Small study only 9 patients gastric vs enteral omeprazole. Efficacy is similar for either route.
Pickworth KK	1993	Occurrence of nosocomial pneumonia in mechanically ventilated trauma patients: a comparison of sucralfate and ranitidine	Crit Care Med. 1993 Dec;21(12):1856-62.	Single center RCT, 83 patients. Comparison sucralfate versus ranitidine. Outcomes: pneumonia.	1	Did not address this question		No difference between sucralfate and ranitidine	2	3 days minimum	3	Small study found no difference between sucralfate and ranitidine RE: pneumonia.
Pimentel M	2000	Clinically significant gastrointestinal bleeding in critically ill patients in an era of prophylaxis.	Am J Gastroenterol. 2000 Oct;95(10):2801-6.	Retrospective review of 7200 patients, identifying 12 with bleeding.	3	Age, septic shock, AAA repair, and enteral or parenteral nutrition	3	No	3	Did not address this question		Risk factors were identified in 12 patients that developed GIB. Did not support SUP.
Prod'hom G	1994	Nosocomial pneumonia in mechanically ventilated patients receiving antacid, ranitidine, or sucralfate as prophylaxis for stress ulcer. A RCT.	Ann Intern Med. 1994 Apr 15;120(8):653-62.	Single center non-placebo controlled RCT, 244 ICU pts. Comparison: antacids, ranitidine, sucralfate. Outcome: GIB, gastric pH, pneumonia	1	Mechanical ventilation	1	Yes, sucralfate	1	until extubated or out of the ICU	2	SUP prophylaxis with sucralfate reduces the risk for late onset pneumonia in vented patients, with similar protection compared to antacids and ranitidine.
Ruiz-Santana S	1991	Stress-induced gastroduodenal lesions and total parenteral nutrition in critically ill patients: frequency, complications and value of prophylactic treatment	Crit Care Med. 1991 Jul;19(7):887-91.	Single center RCT 97 pts on TPN. Comparison: TPN, TPN+sucralfate, TPN+ranitidine. Outcome: GIB.	1	Mechanical ventilation >6 days	2	No	2	Did not address this question		Small study, no difference in GIB while on TPN with or without prophylaxis.
Ryan P	1993	Nosocomial Pneumonia during stress ulcer prophylaxis with cimetidine and sucralfate	Arch Surg. 1993 Dec;128(12):1353-7.	Single center, RCT, 114 pts. Comparison: Cimetidine infusion versus sucralfate. Outcome:GIB, VAP.	1	Did not address this question		No difference between sucralfate and cimetidine	1	Did not address this question		Nice study with decent number of pts, 56 and 58 in each arm but focused on Nosocomial pneumonia and did not define UGI bleed.
Simms H	1991	Role of gastric colonization in the development of pneumonia in critically ill patients	J Trauma. 1991 Apr;31(4):531-6; discussion 536-7.	single center RCT, 89 pts. Comparison: antacids vs cimetidine vs sucralfate. Outcome: Gastric pH, pneumonia.	1	Did not address this question		No	2	ICU stay	2	Small trial, main outcome was pneumonia, no difference between groups
Simons RK	1995	A risk analysis of stress ulceration after trauma	J Trauma. 1995 Aug;39(2):289-93; discussion 293-4.	Retrospective review of trauma patients identifying risk factors, low incidence.	3	ISS >=16, RTS<13, AIS head >=3, SCI	3	Did not address this question.		When risk factors are no longer present, unless SCI then 3 weeks	3	Overall rate of stress ulcer hemorrhage is low, with or without prophylaxis, the SCI population should continue for 3 wks
Thomason MH	1996	Nosocomial pneumonia in ventilated trauma patients during stress ulcer prophylaxis with sucralfate, antacid and ranitidine	J Trauma. 1996 Sep;41(3):503-8.	Single center, RCT, 242 pts. Comparison: Sucralfate, antacid, ranitidine. Outcome: Mortality, GIB, pneumonia.	1	Did not address this question		No, sucralfate equivalent to ranitidine	1	Did not address this question		Antacids associated with higher mortality compared to sucralfate and ranitidine which had equivalent GIB and pneumonia rates.
Zandstra DF	1994	The virtual absence of stress-ulcer related bleeding in ICU patients receiving prolonged mechanical ventilation. A prospective cohort study.	Intensive Care Med. 1994 May;20(5):335-40.	Retrospective study, 183 mixed ICU patients. Comparison: None. Outcome: GIB.	3	Did not address this question		No prophylaxis is necessary	3	Did not address this question		No prophylaxis given, 1% incidence of GIB. Patients were considered high-risk with mean Tryba risk score of 38. All patients received cefotaxime, steroids, and DVT prophylaxis.
Zeltsman D	1996	Is the incidence of hemorrhagic stress ulceration in surgically critically ill patients affected by modern antacid prophylaxis?	Am Surg. 1996 Dec;62(12):1010-3.	Single center retrospective study, 304 pts. Comparison:H2 blockers +/- antacids vs no prophylaxis. Outcome: Hemorrhagic stress ulceration.	3	Did not address this question		No prophylaxis is necessary	3	ICU stay	3	Multidisciplinary ICU with no difference in hemorrhage with or without H2 blockade, does not distinguish if trauma patients had differential stress ulcer hemorrhage.