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To cite this article: Anthony A. Sochet, Sorany Son, Kelsey S. Ryan, Meghan Roddy, Eddie Barrie, Michael Wilsey, Scott D. McKinley & Thomas A. Nakagawa (2019): Stress Ulcer Prophylaxis in Children with Status Asthmaticus Receiving Systemic Corticosteroids: A Descriptive Study Assessing Frequency of Clinically Important Bleeding, Journal of Asthma, DOI: [10.1080/02770903.2019.1614617](https://doi.org/10.1080/02770903.2019.1614617)

To link to this article: <https://doi.org/10.1080/02770903.2019.1614617>



Accepted author version posted online: 02 May 2019.



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Stress Ulcer Prophylaxis in Children with Status Asthmaticus Receiving Systemic Corticosteroids: A Descriptive Study Assessing Frequency of Clinically Important Bleeding

Anthony A. Sochet, MD, MS^{a,b}, Sorany Son, BS^a, Kelsey S. Ryan, MD^{a,c}, Meghan Roddy, PharmD^a, Eddie Barrie^c, Michael Wilsey, MD^{a,b}, Scott D. McKinley, DO^a, Thomas A. Nakagawa, MD^{a,b}

Affiliations: ^aJohns Hopkins All Children's Hospital, St. Petersburg, FL; ^bJohns Hopkins University, School of Medicine, Baltimore, MD; and ^cUniversity of South Florida, Tampa, FL.

Address correspondence to: Anthony Alexander Sochet, MD, MS, Assistant Professor of Anesthesiology and Critical Care Medicine, Division of Pediatric Critical Care Medicine, Johns Hopkins All Children's Hospital, 501 6th Avenue South, OCC Suite 702, Room 709A, [anthony.sochet@jhmi.edu], 727-487-3711.

Keywords: pediatric intensive care unit; gastritis; gastrointestinal bleeding; steroids

Running Head: Stress Ulcer Prophylaxis for Children with Asthma

Stress Ulcer Prophylaxis in Children with Status Asthmaticus Receiving Systemic Corticosteroids: A Descriptive Study Assessing Frequency of Clinically Important Bleeding

Objective: To determine the frequency of clinically important bleeding (CIB) among children hospitalized for status asthmaticus with and without exposure to stress ulcer prophylaxis (SUP).

Methods: We performed a single center, retrospective cohort in 217 children admitted for asthma exacerbation aged 5-18 years from May 2015 to May 2017. We assessed cohorts with and without exposure to SUP to determine if differences in frequency of CIB exist. Study outcomes included frequency of CIB, gastrointestinal complications (occult bleeding, macroscopic bleeding, gastric perforation, and acquired gastritis), and SUP-related adverse events (ventilator associated pneumonia, *C. difficile* colitis, necrotizing enterocolitis, and acute thrombocytopenia).

Results: 92 (42%) children received SUP of which 82 were admitted to the pediatric intensive care unit (PICU). There were no differences in asthma severity or known risk factors for CIB in children with and without SUP in the PICU sub-cohort. We observed no CIB or SUP-related adverse events. Two subjects acquired gastritis in the no-SUP cohort and one additional subject experienced occult gastrointestinal bleeding with spontaneous symptom resolution.

Conclusion

Children admitted for status asthmaticus with and without SUP had no observed incidence of CIB. In this specific population, we propose a prerequisite assessment for the presence of

known stress ulcer related gastrointestinal bleeding risk factors prior to the blanket administration of SUP.

Keywords: pediatric intensive care unit; gastritis; gastrointestinal bleeding; steroids

Accepted Manuscript

Introduction

Stress-related ulceration and gastrointestinal (GI) bleeding among children hospitalized in the pediatric intensive care unit (PICU) occurs as the result of impaired tissue perfusion, loss of mucosal cytoprotection, and erosive, acidic gastric secretions in contact with the enteral epithelium (1). The incidence varies by severity with endoscopic evidence noted in 75-100%, occult bleeding in 15-50% and macroscopic bleeding in 5-25% (1-3). Though minor bleeding is common, clinically important upper GI bleeding (CIB), defined as bleeding associated with an acute drop in serum hemoglobin (<7 mg/dL) or hemorrhagic shock requiring packed red blood cell transfusion, is rare occurring in only 0.1-2.6% of PICU admissions (4-8). Known risk factors for stress-related CIB have been identified and include mechanical ventilation > 48 hours, PICU length of stay (LOS) >7 days, presence of an enteric tube, pre-existing gastroesophagitis, acute kidney injury, known coagulopathy (platelet count $< 50,000$ or INR > 1.5), or exposure to non-steroidal anti-inflammatory (NSAID) agents (2, 7, 9, 10). CIB is of particular interest to hospital-based providers as it is directly associated with prolonged LOS and in-hospital mortality (11).

Children hospitalized with status asthmaticus have been considered at higher risk for stress-related ulceration and GI bleeding from corticosteroid exposure (12). Standard care for status asthmaticus includes the early initiation of systemic corticosteroids to reduce inflammatory dysregulation associated with asthma (13). Consequently, children hospitalized with severe asthma exacerbations are frequently prescribed gastric acid suppression therapy as stress ulcer prophylaxis (SUP) with either histamine-2 blockers (H2B) or proton pump inhibitors (PPI) (14). There is a paucity of epidemiologic data to suggest a risk reduction for CIB from SUP in this specific population (8, 10, 12, 15, 16). In addition, recent publications propose SUP is not benign and may be associated with adverse events such as development of ventilator associated

pneumonia (VAP), *C. difficile* colitis, necrotizing enterocolitis, and acute thrombocytopenia (17-23).

Data supporting the use of SUP for CIB prevention in children with status asthmaticus receiving systemic corticosteroids are sparse and extrapolated from adult populations. We seek to determine the frequency of CIB, GI complications, and SUP-related adverse events among children hospitalized for severe asthma exacerbation with and without exposure to SUP. We hypothesize the overall incidence of CIB is rare and no differences will exist in cohorts with and without SUP exposure.

Materials and methods

Study design and setting

We performed a single center, retrospective cohort study from May 2015 through May 2017 including all children aged 5-18 years with the primary diagnoses of acute asthma exacerbation and/or status asthmaticus. All research activities were conducted within a 259-bed, university-affiliated, tertiary pediatric referral center and included admissions to the general pediatric unit under the hospital medicine service and a 28-bed PICU under the critical care medicine service. Research cohorts were identified by exposure to SUP during hospitalization and initial admission disposition (PICU vs. general pediatric unit). Exclusion criteria included children receiving preadmission H2B/PPI for preexisting gastroesophageal reflux disease, coagulopathy, chronic liver disease, gastroesophagitis, or chronic NSAID use. Children < 5 years of age were excluded to create a more homogeneous sample as it is difficult to retrospectively to discriminate asthma from bronchiolitis in younger children. This study was reviewed and approved by our local institutional review board.

Study outcomes and definitions

The primary study outcomes were (1) frequency of CIB, defined as bleeding associated with a reduction of serum hemoglobin (< 7 mg/dL), concurrent acute hypotension requiring intravenous volume resuscitation (isotonic fluid bolus ≥ 20 ml/kg), or hemorrhagic shock requiring packed red blood cell (pRBC) transfusion, and (2) GI complications including occult gastric bleeding (determined by positive heme-occult testing), radiographically-confirmed gastric perforation, or symptomatic gastritis. Secondary outcomes included frequency of SUP-related adverse events such as VAP, *C. difficile* colitis, necrotizing enterocolitis, or acute thrombocytopenia (platelet count $< 50,000$ cells/mL). Descriptive data included demographics,

comorbidities, pediatric asthma severity scores (PASS, Figure 1), National Heart Lung and Blood Institute (NHLBI) asthma severity classification, inpatient medication use (e.g. terbutaline, magnesium sulfate, ketamine, aminophylline, montelukast, subcutaneous epinephrine, and continuous inhaled albuterol), respiratory therapeutic interventions (e.g. oxygen supplementation, non-invasive ventilation (NIV) use [e.g. bilevel positive airway pressure, continuous positive airway pressure, or heated, humidified, high flow nasal cannula], inhaled helium or mechanical ventilation), extracorporeal membrane oxygenation (ECMO), hospital LOS, PICU LOS, and in-hospital mortality (24, 25). Primary outcomes were noted either directly by hospital billing and physician documentation or indirectly by documented serum hemoglobin, presence of pRBC transfusion, or the administration of medications historically applied in the acute management of upper GI bleeding (e.g. sucralfate, PPI infusions, or octreotide). Additional data collected included discontinuation timing of SUP therapy, if discontinuation coincided with initiation of enteral nutrition (within 6 hours) or transfer from the PICU to the general pediatric unit, if SUP was prescribed at hospital discharge concurrently with enteral corticosteroids, and individual charges for hospital SUP derived from our internal billing database (charges for drugs only, not fees associated with their administration).

Description of institutional asthma-practice

Children admitted for acute asthma exacerbation in our center follow a status asthmaticus clinical pathway. Interventions requiring higher level monitoring such as NIV, continuous albuterol nebulization, vasoactive agents, inhaled helium, or mechanical ventilation are done so in the PICU with collaborative pediatric pulmonology consultation. Inpatient level of care is determined by our emergency department (ED) providers in collaboration with intensive care and hospitalist subspecialties. Transfer to a lower level of care is encouraged once nebulized

albuterol treatments are reduced to every 2 hours and no other PICU-level interventions are anticipated. Stress ulcer prophylaxis included H2Bs such as enteral ranitidine (1-2mg/kg/dose every 12 hours with a maximum of 150mg per dose) or intravenous famotidine (0.5mg/kg per dose every 12 hours with a maximum of 20mg per dose). Corticosteroids included 1-2mg/kg/day of enteral prednisolone / prednisone or 2-4mg/kg/day of intravenous methylprednisolone.

Data collection

Subjects were identified by our local Health Informatics department that queried our database warehouse for billing and patient information for the primary admission diagnoses and presence of at least two PASS values documented during hospitalization. Discrete and explicit data fields were electronically compiled from an internal data warehouse and the Virtual PICU Systems© databases (Virtual PICU Systems, LLC, Los Angeles, CA). Any remaining data deficits were extracted by research team members through manual chart review.

Statistical plan

Descriptive data are reported as proportions, means $\pm$ standard deviation, or medians (IQR, interquartile range) depending on data type and variance. Data distributions were assessed using the Shapiro-Wilk test. Subsequent comparative statistics included Fisher's exact, student's *t*, Wilcoxon rank-sum, and paired testing where appropriate. Type I error was set at 0.05 and all comparative tests were two-sided. All analyses were completed using Stata© v15.1 software (Stata, College Station, TX).

Results

Sampling and general characteristics

During the study period, 217 children met study inclusion and exclusion criteria (Figure 2). Of those 42% (n = 92) received SUP during admission. Children who received SUP were given a H2B and no child in our sample received a PPI. Of the 217, 43% (n = 94) were admitted to the PICU. General sample and PICU subcohort descriptive characteristics can be found in **Table 1**. Our study sample had a mean age of 8.5 ± 3.4 years, mean weight of 35.7 ± 19.3 kilograms, body mass index of 19 ± 5.2 , male:female ratio of 1.5:1, median admission PASS score of 8 (IQR: 5-10), and majority (59%) with a NHLBI severity classification of intermittent or mild-persistent asthma. Children who received SUP had a higher frequency of admission to the PICU (89% vs. 10%, $P < 0.01$), lower rate of intermittent asthma NHLBI classification (23% vs. 40%, $P < 0.01$), and greater admission median PASS values (10 [IQR:6-10] vs 6 [IQR:4-8], $P < 0.01$).

Primary and secondary study outcomes

In our sample, we observed no CIB or gastric perforation. Two children (0.9%) had acquired gastritis by clinical examination of which one (0.5%) was found to have occult GI bleeding. Neither of these subjects received SUP during hospitalization or required treatment interventions for gastritis other than monitoring. Spontaneous resolution of symptoms occurred in both patients prior to hospital discharge without administration of H2B or PPI. Regarding secondary outcomes, we observed no incidence of VAP, *C. difficile* colitis, necrotizing enterocolitis, or acute thrombocytopenia. General study outcomes and other known risk factors for CIB for the entire sample and PICU subcohort can be found in **Table 2**. In the PICU cohort, no differences were noted in length of stay, applied respiratory therapies, medication

administration, or known risk factors for CIB for those patients receiving or not receiving SUP. We observed no in-hospital mortality or use of ECMO for severe asthma exacerbation.

Additional SUP data

Sixty-four (70%) children had SUP discontinued during hospitalization of which 74% occurred upon the initiation of enteral nutrition. The remaining 26% had SUP discontinued at the time of hospital discharge. Upon discharge medication reconciliation, 178 children (82%) received a prescription for extended corticosteroid treatment as an outpatient. Interesting, only 21 of those 178 (12%) also received a prescription for concurrent outpatient SUP. Total SUP charges amounted to a median of \$1 029 (IQR: \$564-\$1 701) per admission.

Discussion

In this retrospective, descriptive cohort study of 217 children admitted for acute asthma exacerbation receiving systemic corticosteroids, we observed no frequency of CIB. These data representing two years of asthma admissions in our institution and highlight the rare incidence of CIB for this population. We noted only minor GI complications regardless of exposure to SUP, *nil per os* status, or asthma severity. A majority of the 92 children who received SUP were admitted to the PICU (89%) without an alternative indication for SUP (e.g. preexisting coagulopathy, nasogastric tube placement, or prolonged mechanical ventilation) suggesting a significant disparity among practice patterns between critical care and hospitalist providers in our institution. The use of H2B in our sample were uncomplicated without incidence of drug related adverse events. There are no published guidelines for pediatric patients with status asthmaticus recommending the use of SUP secondary to exposure from corticosteroids and this report is the first to specifically assess SUP utility, CIB, and GI complications in this population.

The premise for SUP in children with status asthmaticus is based on concerns that systemic corticosteroid exposure, in combination with asthma-related hypoxemia, severe acidosis, low gastric pH, and impaired mucosal cytoprotection, leads to gastric epithelial injury and ulceration. If ulceration were to occur adjacent to blood vessels, potential gastric hemorrhage could ensue. Narum et al (12) performed a systematic review and meta-analysis of the risk of upper GI bleeding from corticosteroid exposure including over 33,000 adults with overall incidence of acute GI bleeding noted in 2.9 % for those on corticosteroids and 2% for placebo. While their meta-analyses yielded an odds ratio (OR) of 1.43 (95% CI: 1.22-1.66) for bleeding events in all patients, subanalyses by indication for corticosteroid use including pulmonary disease showed no association (OR 1.7 [95% CI:0.55-5.22]) and documented “gastroprotective

drugs” were not found to reduce gastric bleeding (OR 1.29 [0.62-2.69]). In a systematic review of SUP use in the PICU setting, Reveiz and colleagues (10) noted the presence of any antacid therapy or sucralfate were not associated with death, endoscopic evidence of gastric ulceration, or incidence of upper GI bleeding. In a randomized, clinical trial of PPI versus placebo by Alhazzani and colleagues (25) the frequency of upper GI bleeding was no greater in those receiving SUP and there was a trend towards increased VAP and *C. difficile* infection in the PPI cohort. A multi-network analysis also by Alhazzani (17) supported a potential association between SUP with PPIs and VAP. In a recent multicenter, randomized controlled trial by Krag et al (26), no differences were noted in CIB in adult ICU patients with and without exposure to pantoprazole. In sum, the scarcity of pediatric data, mounting data from adult trials suggesting the lack of SUP efficacy, and our study results emphasize how pediatric providers must weigh the risk and benefit of potentially unnecessary exposure to SUP without an existing concurrent, established indication.

In other disorders where systemic corticosteroids are indicated, there exists variability in SUP prescribing. For example, children admitted for status asthmaticus are typically placed on either 1-2mg/kg/day of enteral prednisolone / prednisone or 2-4mg/kg/day of intravenous methylprednisolone (13, 27). Yet, in the treatment of acute rheumatologic flairs, autoimmune disease, or acute infantile spasms the doses of pulse steroids such as methylprednisolone reach as high as 1 gram/day, 4-20 times a typical dose for status asthmaticus (28-30). Pulse steroid doses are routinely administered without recommendation for SUP or an elevated incidence of acute GI complications. One of the most striking examples of discrepant recommendations for SUP exist in the management of pediatric inflammatory bowel diseases, such as Crohn’s disease or ulcerative colitis. The hallmark symptom of these disorders is development of GI ulceration

typically treated with a combination of immunomodulators including pulse corticosteroids (31, 32). Yet, there are no recommendations for routine concurrent SUP in chronically corticosteroid exposed children with severe and acute GI ulcerative disease.

The provision of enteral nutrition alone may be as effective as pharmacologic SUP. Huang et al (33) noted in a meta-analysis that among patients receiving enteral nutrition, the addition of SUP did not reduce CIB and was associated with hospital-acquired pneumonia (RR 1.53 (95%CI: 1.04-2.27)). These findings were consistent with contemporaneous publications supporting the concept of enteral nutrition as SUP to prevent CIB (34). In our manuscript, we noted 51% of children had SUP discontinued upon initiation of enteral nutrition and an additional 17% were discontinued at hospital discharge. It is unclear if hospitalist providers elected simply to not continue SUP after initiation of enteral nutrition or if they believed enteral nutrition acted as non-pharmacologic SUP, improved GI perfusion, and enhanced cytoprotective mechanisms.

One would expect if a clinician was concerned enough to prevent CIB with SUP, they would order tests to assess for known risk factors for GI bleeding such as thrombocytopenia or coagulopathy. Yet, only 47% of our sample had a complete blood count drawn of which the mean platelet count was $292,000 \pm 85,000$ cells/mL. Four subjects (1.8%) had clotting times ordered. Considering other risks for CIB, only 3% (7/217) were intubated and all but two for less than 48 hours. The PICU LOS was less than 7 days in 99% (91/92 subjects). Other risk factors include poor perfusion and oxygenation to the GI tract. Nearly 40% of patients in our study required oxygen supplementation with either a simple mask or regular nasal cannula and one subject was on an epinephrine infusion that may infer impaired gut perfusion. In sum, 4/217

(1.8%) children had clear alternative indications for SUP beyond corticosteroid exposure for their asthma exacerbation.

From an economic perspective, charges associated with SUP amounted to a median of just over \$1 000 dollars per admission. Collectively these charges totaled \$150 509. While these fees may pale in comparison to total hospitalization charges, there are an estimated 200 000 admissions for pediatric status asthmaticus annually in the United States (35-37). Although cost to charge ratios vary by institution and region, the fiscal impact of potentially unnecessary SUP on a national level is likely not insignificant.

Limitations

Given the low frequency of gastritis and CIB, this study is underpowered to assess predictive factors and limited to descriptive analyses. As there is a paucity of data in pediatrics and specifically asthma, the completion of a systematic review and metaanalysis are not currently achievable. The retrospective nature of this study limits our ability to determine causality, the exact indication for SUP, and definitive identification of study outcomes. Most children in our sample receiving SUP were admitted to the PICU, had a longer LOS, and greater asthma severity. Compared to the group of PICU patients who did not receive SUP, we did not detect any major differences. However, one could conclude that the reason we did not observe any sizable frequency of CIB, GI complications, or SUP-related adverse events was the provision of SUP itself. To create a more homogeneous sample of children receiving SUP only for corticosteroid exposure, we excluded children already prescribed a H2B/PPI or with an alternative indication for SUP. Yet, these exclusions unlikely confound our study observations. A multicenter randomized trial or large database query is needed to empower national guideline development and institutional protocol changes. While we sought to assess rate of CIB, we did

not perform screening upper endoscopy or heme-occult stool testing on all subjects as the procedural and anesthetic risk is too great. It may be that occult ulceration was underreported due to the retrospective nature of this study. Asthma and SUP practice may vary across and within institutions thus limiting the generalizability of these data. However, our data likely represents similar experiences of tertiary pediatric referral centers.

Conclusions

We present a comparative study specifically addressing the incidence of CIB to assess the utility of SUP in children hospitalized with status asthmaticus receiving systemic corticosteroids. SUP was commonly administered in our institution (92/217, 42%) and disparately within the PICU sub-cohort (82/92, 89%). We observed no incidence of CIB, only minimal frequency of gastritis (1%), and no SUP-related adverse events. Providers discontinued SUP in nearly 70% of cases, typically after initiation of enteral nutrition. Our findings suggest the blanket prescription of SUP for children with asthma exacerbation receiving systemic corticosteroids demands further review. At this time, more judicious approach should include a targeted assessment of known stress ulcer and CIB risk factors such as preexisting coagulopathy, prolonged intubation, and compromised hemodynamics / perfusion before administering SUP.

Acknowledgments

None

Declaration of Interests Statements

Financial Disclosure: Dr. Nakagawa receives author royalties from Wolters Kluwer, UpToDate© and was a consultant for Fresenius Kabi. The remaining authors have indicated they have no financial relationships relevant to this article to disclose.

Conflicts of Interest: The authors have indicated they have no potential conflicts of interest to disclose.

References

1. Ali T, Hart RF. Stress-induced ulcer bleeding in critically ill patients. *Gastroenterol Clin North Am* 2009;38(2):245-265.
2. Barletta JF, Bruno JJ, Buckley MS, Cook DJ. Stress ulcer prophylaxis. *Crit Care Med* 2016;44(7):1395-1405.
3. Faisy C, Guerot E, Diehl JL, Iftimovici E, Fagon JY. Clinically significant gastrointestinal bleeding in critically ill patients with and without stress-ulcer prophylaxis. *Intensive Care Med* 2003;29(8):1306-1313.
4. Chaibou M, Tucci M, Dugas MA, Farrell CA, Proulx F, Lacroix J. Clinically significant upper gastrointestinal bleeding acquired in a pediatric intensive care unit: a prospective study. *Pediatrics* 1998;102(4 Pt 1):933-938.
5. Lacroix K, Nadeau D, Laberge S, Gauthier M, Lapierre G, Farrell CA. Frequency of upper gastrointestinal bleeding in a pediatric intensive care unit. *Crit Care Med* 1992;20(1):35-42.
6. Costarino AT, Dai D, Feng R, Feudtner C, Guevara JP. Gastric acid suppressant prophylaxis in pediatric intensive care: current practice as reflected in a large administrative database. *Pediatr Crit Care Med* 2015;16(7):605-612.
7. Cook DJ, Fuller HD, Guyatt GH, Marshall JC, Leasa D, Hall R, Winton TL, Rutledge F, Todd TJ, Roy P, et al. Risk factors for gastrointestinal bleeding in critically ill patients. Canadian Critical Care Trials Group. *N Engl J Med* 1994;330(6):377-381.
8. Krag M, Perner A, Wetterslev J, Wise MP, Borthwick M, Bendel S, McArthur C, Cook D, Nielsen N, Pelosi P, et al. Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients. *Intensive Care Med* 2015;41(5):833-845.

9. Cook D, Heyland D, Griffith L, Cook R, Marshall J, Pagliarello J. Risk factors for clinically important upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. Crit Care Med 1999;27(12):2812-2817.
10. Reveiz L, Guerrero-Lozano R, Camacho A, Yara K, Mosquera PA. Stress ulcer, gastritis, and gastrointestinal bleeding prophylaxis in critically ill pediatric patients: a systematic review. Pediatr Crit Care Med 2010;11(1):124-132.
11. Cook DJ, Griffith LE, Walter SD, Guyatt GH, Meade MO, Heyland DK, Kirby A, Tryba M; Canadian Critical Care Trials Group. The attributable mortality and length of intensive care unit stay of clinically important gastrointestinal bleeding in critically ill patients. Crit Care 2001;5(6):368-375.
12. Narum S, Wetergren T, Klemp M. Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis. BMJ Open 2014;4(5):e004587.
13. Chung KF. Diagnosis and management of severe asthma. Semin Respir Crit Care Med 2018;38(1):91-99.
14. Joret-Descout P, Dager S, Bellaicher M, Bourdon O, Prot-Labarthe S. Guidelines for proton pump inhibitor prescriptions in paediatric intensive care unit. Int J Clin Pharm 2017;39(1):181-186.
15. Krag M, Perner A, Wetterslev J, Wise MP, Hylander-Moller M. Stress ulcer prophylaxis versus placebo or no prophylaxis in critically ill patients. A systematic review of randomised clinical trials with meta-analysis and trial sequential analysis. Intensive Care Med 2014;40:11-22.
16. Marker S, Perner A, Wetterslev J, Barbateskovic M, Jakobsen JC, Krag M, Granholm A, Anthon CT, Møller MH. Stress ulcer prophylaxis versus placebo or no prophylaxis in adult

hospitalised acutely ill patients-protocol for a systematic review with meta-analysis and trial sequential analysis. *Syst Rev* 2017;5(1):118

17. Alhazzani W, Alshamsi F, Belley-Cote E, Heels-Ansdell D, Brignardello-Petersen R, Alguraini M, Perner A, Møller MH, Rag M, Almenawer S, et al. Efficacy and safety of stress ulcer prophylaxis in critically ill patients: a network meta-analysis of randomized trials. *Intensive Care Med* 2018;44(1):1-11.
18. Binnetoğlu E1, Akbal E, Şen H, Güneş F, Erbağ G, Aşık M, Bozkurt N, Uludağ A, Tekin M, Tekin SZ. Pantoprazole-induced thrombocytopenia in patients with upper gastrointestinal bleeding. *Platelets* 2015;26():10-12.
19. Buendgens L, Bruensing J, Matthes M, Dückers H, Luedde T, Trautwein C, Tacke F, Koch A. Administration of proton pump inhibitors in critically ill medical patients is associated with increased risk of developing *Clostridium difficile*-associated diarrhea. *J Crit Care* 2014;29(4):696, e11-e15.
20. Ro Y, Eun CS, Kim HS, Kim JY, Byun YJ, Yoo KS, Han DS. Risk of *clostridium difficile* infection with the use of a proton pump inhibitor for stress ulcer prophylaxis in critically ill patients. *Gut Liver* 2016;10(4):581-586.
21. Terrin G, Passariello A, De Curtis M, Manguso F, Salvia G, Lega L, Messina F, Paludetto R, Canani RB. Ranitidine is associated with infections, necrotizing enterocolitis, and fatal outcome in newborns. *Pediatrics* 2012;129(1):e40-e45.
22. Azab M, Doo L, Doo DH, Elmofti Y, Ahmed M, Cadavona JJ, Liu XB, Shafi A, Joo MK, Yoo JW. Comparison of the hospital-acquired *Clostridium difficile* infection risk of using proton pump inhibitors versus histamine-2 receptor antagonists for prophylaxis and treatment of stress ulcers: a systematic review and meta-analysis. *Gut Liver* 2017;11(6):781-788.

23. Barletta JH, Sclar DA. Proton pump inhibitors increase the risk for hospital-acquired *Clostridium difficile* infection in critically ill patients. *Crit Care* 2014;18(6):714.
24. Gorelick MH, Stevens MW, Schultz TR, Scribano PV. Performance of a novel clinical score, the Pediatric Asthma Severity Score (PASS), in the evaluation of acute asthma. *Acad Emerg Med* 2004;11(1):10-18.
25. Alhazzani W, Guyatt G, Alshahrani M, Deane AM, Marshall JC, Hall R, Muscedere J, English SW, Lauzier F, Thabane L, et al; Canadian Critical Care Trials Group. Withholding pantoprazole for stress ulcer prophylaxis in critically ill patients: a pilot randomized clinical trial and meta-analysis. *Crit Care Med* 2017;45(7):1121-1129.
26. Krag M, Marker S, Wetterslev J, Wetterslev J, Wise MP, Schefold JC, Keus F, Guttormsen AB, Bendel S, Borthwick M; SUP-ICU Trial Group. Pantoprazole in patients at risk for gastrointestinal bleeding in the ICU. *N Engl J Med*, 2018; doi: 10.1056/NEJMoa1714919. [Epub ahead of print].
27. National Heart Lung and Blood Institute. Guidelines for the diagnosis and management of asthma (EPR-3). Accessed on August 1st, 2018. < <https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma>>
28. Parker BJ, Bruce IN. High dose methylprednisolone therapy for the treatment of severe systemic lupus erythematosus. *Lupus* 2007;16(6):387-393.
29. Newburger JW. Kawasaki disease: medical therapies. *Congenit Heart Dis* 2017;12(5):641-643.
30. Yeh HR, Kim MJ, Ko TS, Yum MS, You SJ. Short-term outcome of intravenous methylprednisolone pulse therapy in patients with infantile spasms. *Pediatr Neurol* 2017;71:50-55.

31. Ruemmele FM, Veres G, Kolho KL, Griffiths A, Levine A, Escher JC, Amil Dias J, Barabino A, Braegger CP, Bronsky J, et al; European Crohn's and Colitis Organisation; European Society of Pediatric Gastroenterology, Hepatology and Nutrition. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. *J Crohns Colitis* 2014;8(10):1179-1207.
32. Rosen MJ, Dhawan A, Saeed SA. Inflammatory bowel disease in children and adolescents. *JAMA Pediatr* 2015;169(11):1053-1060.
33. Huang HB, Jiang W, Wang CY, Qin HY, Du B. Stress ulcer prophylaxis in intensive care unit patients receiving enteral nutrition: a systematic review and meta-analysis. *Crit Care* 2018;22(1):20.
34. Nourian A, Mohammadi M, Beigmohammadi MT, Taher M, Dadvar Z, Malekolkottab M, Ramezani M, Khalili H. Comparing efficacy of enteral nutrition plus ranitidine and enteral nutrition alone as stress ulcer prophylaxis. *J Comp Eff Res* 2018;7(5):493-501.
35. United States Center for Disease Control and Prevention. Most recent asthma data: national current asthma prevalence (2014). Accessed on 2 February 2017.
<https://www.cdc.gov/asthma/most_recent_data.htm>
36. Fassl BA, Nkoy FL, Stone BL, Srivastava R, Simon TD, Uchida DA, Koopmeiners K, Greene T, Cook LJ, Maloney CG. The joint commission children's asthma care quality measures and asthma readmissions. *Pediatrics* 2012; 130(3):482-491.
37. Akinbami LJ, Moorman JE, Garbe PL, Sondik EJ. Status of childhood asthma in the United States, 1980-2007. *Pediatrics* 2009;123(Suppl 3):S131-145.

Table 1. General study sample and pediatric intensive care unit subcohort descriptive characteristics.

Characteristics	Entire Study Sample (n = 217)			PICU Subcohort (n = 94)		
	SUP + (n=92)	SUP - (n=125)	<i>P</i>	SUP + (n=82)	SUP - (n=12)	<i>P</i>
Age, years $\pm$ SD	8.8 $\pm$ 3.8	8.3 $\pm$ 3.2	0.34	8.4 $\pm$ 3.6	8.5 $\pm$ 3.6	0.97
Weight, kilograms $\pm$ SD	38.8 $\pm$ 22.1	33.4 $\pm$ 16.8	0.04	29.2 $\pm$ 5.8	31.2 $\pm$ 7.2	>0.99
Gender ratio, male:female	1.4:1	1.5:1	0.89	1.4:1	0.7:1	>0.99
NHLBI category, <i>n</i> (%)						
Intermittent	21 (23%)	50 (40%)	<0.01	18 (22%)	4 (33%)	0.47
Persistent, mild	26 (28%)	30 (24%)	0.53	26 (32%)	2 (17%)	0.5
Persistent, moderate	38 (41%)	39 (31%)	0.15	32 (39%)	5 (42%)	>0.99
Persistent, severe	7 (8%)	6 (5%)	0.4	6 (7%)	1 (8%)	>0.99
Admit PASS, median (IQR)	10 (6-10)	6 (4-8)	<0.01	10 (8-12)	11 (8-12)	0.8
Comorbid pneumonia, <i>n</i> (%)	16 (17%)	8 (6%)	0.02	15 (18%)	0 (0%)	0.2
Comorbid obesity, <i>n</i> (%)	14 (15%)	10 (8%)	0.13	12 (15%)	2 (17%)	>0.99

IQR = interquartile range; NHLBI = National Heart Lung and Blood Institute; PASS = pediatric asthma severity score; PICU = pediatric intensive care unit; SD = standard deviation; SUP = stress ulcer prophylaxis

Table 2. General study outcomes and known risk factors for CIB for the entire study sample and pediatric intensive care unit sub-cohort.

Characteristics	Entire Study Sample (n = 217)			PICU Subcohort (n = 94)		
	SUP + (n=92)	SUP - (n=125)	P	SUP + (n=82)	SUP - (n=12)	P
Length of stay, <i>day (IQR)</i>						
Hospital	2.1 (1.5-3.1)	1.1 (0.8-1.7)	<0.01	2.2 (1.6-3.2)	1.0 (1.4-2.4)	0.21
PICU	--	--	--	1 (0.7-1.9)	1 (0.7-1.3)	0.39
Mortality, <i>n (%)</i>	0 (0%)	0 (0%)	>0.99	0 (0%)	0 (0%)	>0.99
Medication use, <i>n (%)</i>						
Ipratropium	85 (92%)	114 (91%)	0.81	76 (93%)	11 (92%)	>0.99
Magnesium sulfate	74 (80%)	41 (33%)	<0.01	69 (84%)	8 (67%)	0.22
Subcutaneous epinephrine	8 (9%)	1 (1%)	<0.01	8 (10%)	0 (0%)	0.59
Montelukast	20 (22%)	28 (22%)	>0.99	19 (23%)	2 (17%)	>0.99
Continuous albuterol	--	--	--	77 (94%)	9 (75%)	0.06
Terbutaline	--	--	--	10 (11%)	9 (0%)	0.59
Aminophylline	--	--	--	0 (0%)	0 (0%)	>0.99
Ketamine	--	--	--	5 (5%)	0 (0%)	>0.99
Respiratory therapies, <i>n (%)</i>						
Regular nasal cannula	42 (46%)	46 (39%)	0.21	40 (49%)	8 (67%)	0.36
Simple face-mask	61 (66%)	25 (20%)	<0.01	59 (72%)	7 (58%)	0.33
Inhaled helium	--	--	--	4 (5%)	0 (0%)	>0.99
Non-invasive ventilation	--	--	--	15 (18%)	2 (17%)	>0.99
Mechanical ventilation	--	--	--	7 (9%)	0 (0%)	0.58
ECMO	--	--	--	0 (0%)	0 (0%)	>0.99
Known CIB risk factors						
Platelet count, <i>mean ± SD</i>	287 ± 81	299 ± 90	>0.99	287 ± 82	316 ± 139	0.48
<50,000 cells/mL, <i>n (%)</i>	0 (0%)	0 (0%)	>0.99	0 (0%)	0 (0%)	>0.99
INR < 1.5, <i>n (%)</i>	0 (0%)	0 (0%)	>0.99	0 (0%)	0 (0%)	>0.99
Nasoenteric tube, <i>n (%)</i>	8 (9%)	0 (0%)	<0.01	8 (0%)	0 (0%)	0.59
LOS > 7 days, <i>n (%)</i>	4 (2%)	0 (0%)	>0.99	4 (5%)	0 (0%)	>0.99
Intubation > 48hr, <i>n (%)</i>	--	--	--	2 (2%)	0 (0%)	>0.99

CIB = clinically important upper gastrointestinal bleeding; ECMO = extracorporeal membrane oxygenation; INR = international normalized ratio; IQR = interquartile range; LOS = length of stay; PICU = pediatric intensive care unit; SD = standard deviation; SUP = stress ulcer prophylaxis

Figure Legends

Score	0	1	2	3
Respiratory rate				
2 - 3 years of age	≤ 26	27 - 34	35 - 39	≥ 40
4 - 5 years of age	≤ 24	25 - 30	31 - 35	≥ 36
6 - 12 years of age	≤ 20	21 - 26	27 - 30	≥ 31
> 12 years of age	≤ 18	19 - 23	24 - 27	≥ 28
Oxygen requirement	$\geq 98\%$ on room air	95-97% on room air	90 - 94% on room air	< 90% on room air or on supplemental O ₂
Auscultation	Normal aeration	Minimal end-expiratory wheezing	Notable expiratory wheezing	Inspiratory + expiratory wheezing, or diminished breaths
Retractions	None	1 site	2 sites	≥ 3 sites
Dyspnea	None	Speaks in sentences, coos and babbles	Partial sentences, short cry	Single words, short phrases, grunting

Figure 1. Pediatric Asthma Severity Score adapted from Gorelick et al (24).

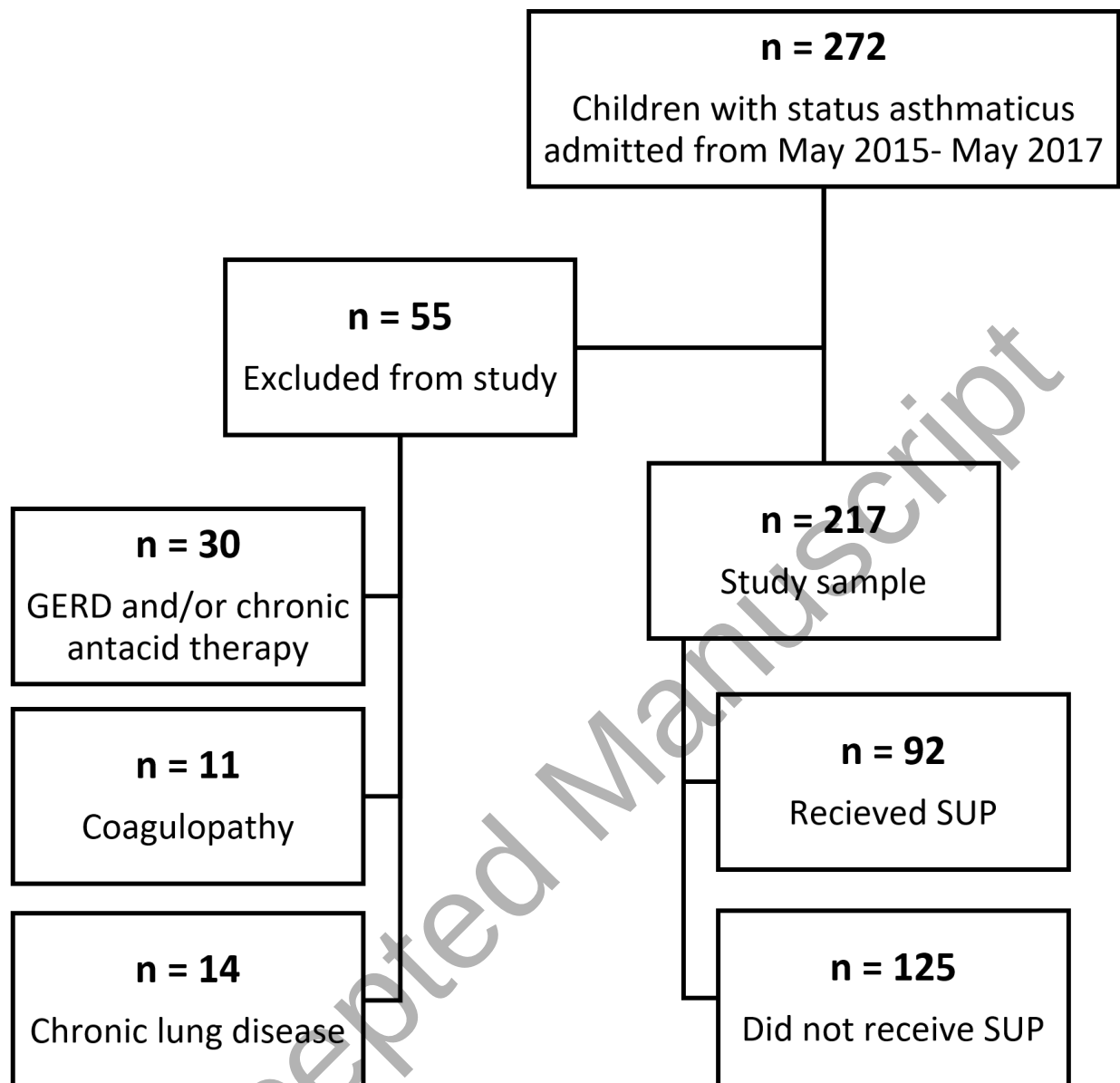


Figure 2. Study sampling description.