CQR is a recurring section in Hospital Pediatrics where authors start with a relevant clinical question, find and synthesize the recent literature and provide their best answer to the question in conclusion.

Are there risks associated with empiric acid suppression treatment of infants and children suspected of having gastroesophageal reflux disease?

abstract

BACKGROUND: It has become common practice to empirically treat infants and children who have suspected gastroesophageal reflux disease by using acid-suppressive medications. However, evidence to support the effectiveness of these medications in the pediatric population is limited. With multiple studies in adult patients indicating increased risk of infection, we reviewed the literature to determine the association between acid-suppressive medications and serious adverse effects in infants and children.

METHODS: We conducted a PubMed search on the adverse effects of H_2 antagonists and proton pump inhibitors in pediatric patients. The studies selected were original research and systematic reviews with control groups and study objectives evaluating the relationship between acid-suppressive medications and serious adverse effects (namely, infections).

RESULTS: Fourteen studies met our inclusion criteria. The majority of studies found a significant association between acid-suppressive medications and the risk of necrotizing enterocolitis, sepsis/bacteremia, pneumonia, and gastrointestinal infections in infants and children.

CONCLUSIONS: Given the questionable efficacy of H_2 antagonists and proton pump inhibitors and the growing evidence of increased risk of serious infections, acid-suppressive medications should be used cautiously in infants and children suspected of having gastroesophageal reflux disease.

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KEY WORDS
acid suppression, drug safety, gastroenteritis, infections, pneumonia

ABBREVIATIONS
CDAD: *Clostridium difficile*–associated disease
CI: confidence interval
GERD: gastroesophageal reflux disease
NEC: necrotizing enterocolitis
OR: odds ratio
PPI: proton pump inhibitor
VAP: ventilator-associated pneumonia

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BACKGROUND

The diagnosis of gastroesophageal reflux disease (GERD) is challenging, and, as clinicians, we are often poor at clinically determining who has GERD and who does not. In a group of infants referred to a gastroenterology clinic for persistent regurgitation, only 1 of 5 had evidence of abnormal esophageal acid reflux on diagnostic testing.[1] Furthermore, most tests, including esophageal pH monitoring, do not correlate well with symptoms.[2] Clinical practice guidelines developed by experts do not support the routine use of diagnostic testing for GERD.[2] As a result, it is common to find patients given a "trial" of acid-suppressive agents and monitored for symptomatic improvement.

In the last 2 decades, we have seen a dramatic increase in the rate of proton pump inhibitor (PPI) use both in adult and pediatric patients.[3] Between 2000 and

2003, there was a fourfold increase in the prevalence of PPI use in infants, with an estimated 7.5-fold increase from 1999 to 2004.[4] In 1 gastrointestinal subspecialty clinic, the referrals for regurgitation nearly doubled from 14% to 23%, and 85% of these referred infants were already started on acid-suppressive medications before evaluation by the gastroenterologist.[1]

As the use of acid-suppressive medication has increased, many have questioned the effectiveness and safety of these agents. Although suppression may be effective in the treatment of rare, severe erosive GERD in children,[5] more recent studies have questioned the effectiveness of acid suppression in the many cases of indiscriminantly diagnosed GERD. In a review of 5 placebo-controlled studies, 4 demonstrated that PPIs were no more effective than placebo in reducing symptoms in infants.[6–10] No placebo-controlled study in children aged >1 year was identified. However, among this older group, several studies compared different doses of PPI or PPIs with other antireflux medications. In general, these studies found that PPIs were no more effective in reducing GERD symptoms from baseline when compared with other doses and other antireflux medications.[11–15]

In addition to questions of effectiveness, concerns regarding the safety of these agents have been raised. Multiple studies in adult patients have found an association between acid-suppressive medications and infectious diseases (pneumonia and gastrointestinal infections) and noninfectious ailments (hip fractures and vitamin B_{12} deficiency).[3,16–26] These findings challenge our practice of empirical acid-suppressive treatment of suspected GERD in infants and children. The goal of this review was to evaluate the potential serious adverse effects associated with acid-suppressive medications in the pediatric population.

METHODS

We performed a PubMed search for the following key terms: "acid suppression," "proton-pump inhibitors," "histamine H_2 antagonists," "anti-ulcer agents," "pantoprazole," "omeprazole," "lansoprazole," "ranitidine," "famotidine," and "cimetidine." These terms were searched in combination with the following key terms: "adverse effects," "side effects," and "infections." The search was restricted to the pediatric population (birth–18 years) and to the English language. The reference sections of articles were reviewed for additional studies. The studies included in this review were limited to original placebo-controlled studies or comparisons with a nonacid suppression arm, with the stated objective to evaluate the relationship between acid-suppressive medications and serious adverse effects (namely, infections). Withdrawal studies were excluded given the study design to expose all patients to acid-suppressive medications before withdrawal of medication.

RESULTS

Fourteen studies met our inclusion criteria, the majority of which involved the NICU or PICU. These studies were divided into NICU, PICU, and non–critical care pediatric populations, given the inherent differences between these groups (see Table 1).

NICU Population

Necrotizing Enterocolitis

Guillet et al[27] performed a retrospective, case-control study of H_2 antagonists and the incidence of necrotizing enterocolitis (NEC) in very low birth weight infants. Through a database of 19 neonatal research centers, 787 infants with birth weights between 401 and 1500 g and a diagnosis of NEC were identified. Each case of NEC was matched based on birth weight, race, and center with 3 controls without NEC. H_2 antagonist use was documented if ranitidine, famotidine, or cimetidine was received >1 day before the diagnosis of NEC (but not counted if the H_2 antagonist was received later) or before age 4 months, death, or discharge. The study demonstrated that previous use of an H_2 antagonist was associated with a significantly increased risk of NEC (odds ratio [OR]: 1.71 [95% confidence interval (CI): 1.34–2.19], $P < .0001$).

Terrin et al[28] conducted a multicenter, prospective, observational study of very low birth weight infants (401–1500 g) or infants of gestational age between 24 and 32 weeks. Two cohorts, those exposed and those not exposed to ranitidine, were observed over a 1-year period for infections, NEC, and death. Initiation and duration of ranitidine treatment were determined by the care providers at the time who were not aware of the study objectives. Infectious outcomes of sepsis, pneumonia, or urinary tract infections were defined according to clinical signs and positive culture results or radiographic evidence (for pneumonia). Diagnosis of NEC was based on standard clinical and radiologic criteria. Of the 274 infants studied, 91 received ranitidine and 183 did not. The study found that infants exposed to ranitidine were more likely to develop infections, specifically sepsis, urinary tract infections, or pneumonia, compared with infants who were not exposed to ranitidine (OR: 5.5 [95% CI: 2.9–10.4], $P < .001$). In addition, infants

exposed to ranitidine had a significantly increased risk of NEC (OR: 6.6 [95% CI: 1.7–25], $P = .003$) and death ($P = .003$).

Sepsis/Infections

Beck-Sague et al[29] conducted a multicenter, prospective study evaluating risk factors for bloodstream infection in patients in 3 NICUs. Bloodstream infections were defined as clear pathogen isolated in blood culture or common contaminant isolated in repeated blood cultures but associated with symptoms, including temperature instability, apnea, or bradycardia. Of the 376 infants enrolled in the study, 42 (11.2%) had bloodstream infections. Bloodstream infections were significantly associated with very low birth weight, lower gestational age, lower Apgar scores, increased severity of illness at admission, respiratory diagnoses at admission, and receipt of 3 medications, including steroids, theophylline, and H_2 antagonists. When controlling for these variables by logistic regression analysis, only very low birth weight, respiratory diagnoses, and use of H_2 antagonists (OR: 2.9; $P = .008$) were independently associated with bloodstream infections.

Rojas et al[30] conducted a prospective study of infants admitted to 8 NICUs in South America to determine risk factors for nosocomial infections in this population. Nosocomial infection was defined as infection after 72 hours of hospitalization with positive culture results and antibiotic treatment. Of the 1504 eligible infants, 80 were treated for 127 episodes of nosocomial infection. The exact infection was not described in the study. Various maternal and infant risk factors were assessed, and only those that preceded the nosocomial infection were included. On univariate analysis, H_2 antagonists were significantly associated with nosocomial infections (OR: 7.3 [95% CI: 3.9–13.6]). When controlling for other variables through the multivariate regression analysis, H_2 antagonist exposure continued to be a risk factor for nosocomial infection (OR: 3 [95% CI: 1.1–7.7]).

Graham et al[31] conducted a case-control study to examine the risk factors for Gram-negative bacteremia in very low birth weight infants in NICUs. Forty-eight cases of very low birth weight infants with hospital-acquired Gram-negative bacteremia, defined as a clear pathogen isolated in the blood culture after >48 hours of hospitalization, were identified. These cases were matched with 169 controls. Risk factors were retrospectively reviewed from admission until day before first Gram-negative blood culture (for case) or date of discharge or death (for control). Although several risk factors were found to be significantly associated with Gram-negative bacteremia, H_2 antagonists and PPI use trended toward but did not achieve significance (OR: 3.1 [95% CI: 0.96–10.2], $P = .059$).

Bianconi et al[32] performed a single-center, retrospective review examining the association of ranitidine with late-onset sepsis in infants hospitalized in the NICU. Of the 569 infants studied, 53 (9%) were exposed to ranitidine and 74 (13%) developed late-onset sepsis. There was no significant difference in birth weight, gestational age, length of stay, and days receiving parenteral nutrition between the infants with sepsis who received ranitidine and those who did not. Infants with late-onset sepsis were significantly more likely to have received ranitidine compared with those who did not develop late-onset sepsis (OR: 6.99 [95% CI: 3.78–12.94], $P < .0001$).

PICU Population

Ventilator-Associated Pneumonia

Elward et al[33] conducted a prospective cohort study on risk factors associated with ventilator-associated pneumonia (VAP) in PICU patients. Diagnostic criteria for VAP were based on National Nosocomial Infections Surveillance criteria. Of the 595 enrolled patients who were mechanically ventilated, 34 episodes of VAP were identified in 30 patients. On univariate analysis, when comparing mechanically ventilated patients with and without VAP, H_2 antagonists were significantly associated with VAP (47% vs 24%; $P = .006$). Although other variables were also associated with VAP, including severity of illness, genetic syndrome, reintubation, transfusion, transport out of PICU, parenteral nutrition, steroids, central lines, bloodstream infection, and length of stay, the authors did not include H_2 antagonist use in their multiple regression analysis.

Yildizdas et al[34] conducted a prospective randomized controlled study comparing the incidence of VAP among 160 intubated patients in a single PICU who were randomized to receive omeprazole, ranitidine, sucralfate, or nothing as a stress ulcer prophylaxis. The difference in the rate of VAP in the sucralfate (42%), ranitidine (48%), omeprazole (45%), and no treatment (41%) groups was not statistically significant ($P = .963$). While acknowledging that a larger study was warranted, the authors concluded that there was no increased risk of VAP with the use of acid-suppressive therapy compared with no treatment.

Lopriore et al[35] conducted a retrospective study assessing the incidence

of VAP and bacterial colonization of upper airways in children admitted to the PICU. Of the 155 children included in this study, 54 were given ranitidine, 53 were given sucralfate, and 48 were given no stress ulcer prophylaxis. There were significant differences in baseline characteristics among the 3 groups; patients receiving no prophylaxis were more likely to have respiratory illness as the primary diagnosis and a longer duration of intubation. No statistically significant difference was found in the incidence of VAP when comparing the sucralfate (7.5%), ranitidine (11.1%), and no prophylaxis (6.2%) groups. The risk factors associated with VAP included duration of intubation and erythromycin/cisapride use. On logical regression analysis, only the duration of intubation was found to be a significant risk factor for development of VAP ($P = .04$).

Sharma et al[36] conducted a prospective, observational study on the risk factors associated with VAP in children in India. Children between 1 month and 15 years of age requiring ventilatory support for at least 48 hours in a PICU were observed for development of VAP. Diagnostic criteria for VAP were based on standards from previous studies. Of the 40 enrolled patients, 8 developed VAP. A number of different variables, including use of ranitidine, transfusions, central line insertion, reintubations, feeding on a ventilator, steroids, and admission clinical status, were analyzed to determine the association between these variables and VAP. Ranitidine was given in 5 (62.5%) of 8 children who developed VAP and 7 (21.9%) of 32 children who did not develop VAP. Of all the variables, the use of ranitidine for at least 2 days was the only statistically significant risk factor associated with the development of VAP ($P = .025$).

Other

Singh-Naz et al[37] conducted a prospective, observational study of risk factors associated with nosocomial infections in patients in the PICU over a 1-year period. Assessed variables included age, mortality risk, immune status, H_2 antagonist use, parenteral nutrition, and length of stay. Of the 945 admitted children, 96 developed nosocomial infections. During the univariate analysis, H_2 antagonist use was significantly higher in children with nosocomial infections compared with those without nosocomial infections (49.3% vs 24.6%; $P < .0001$). With multivariate logistic regression analysis, however, H_2 antagonist use was no longer a significant risk factor for nosocomial infection.

Non–Critical Care Pediatric Population

Pneumonia

Canani et al[38] performed a prospective cohort study of children between the ages of 4 and 36 months, across 4 pediatric gastroenterology centers, to evaluate the association of acid-suppressive medications with acute gastroenteritis or pneumonia. Children referred for GERD-like symptoms were diagnosed with GERD according to results of esophageal pH monitoring and esophageal biopsy. One-half of this cohort received omeprazole (1 mg/kg per day) and the other half received ranitidine (10 mg/kg per day) for a 2-month course. Only children who demonstrated symptomatic resolution, suggesting medicine compliance, were included in the study. These children were matched with healthy controls who had no exposure to acid-suppressive medications before study enrollment. During the 4-month follow-up period, 11 (12%) of the 91 patients who received acid suppression and 2 (2%) of the 95 control patients developed pneumonia. This finding demonstrates a statistically significant increase in the rate of pneumonia in children receiving acid suppression ($P < .05$). In the logistic regression analysis, children exposed to acid-suppressive medications were still significantly more likely to develop pneumonia than the control group (OR: 6.39 [95% CI: 1.38–29.7]).

Orenstein et al[6] conducted a multicenter, prospective study evaluating the efficacy and safety of PPIs in infants. Infants between 28 days and 12 months of age with symptomatic GERD unresponsive to conservative therapy were included. Eighty-one infants were randomized to receive lansoprazole, and the other 81 infants were randomized to the placebo group. In addition to evaluating the efficacy of lansoprazole, the study also evaluated safety through reported adverse events and laboratory data. Although not all events were associated with lansoprazole, serious adverse events were significantly associated with lansoprazole compared with placebo (12% vs 2%; $P = .032$), with lower respiratory tract infection as the leading serious event observed.

Gastrointestinal Infections

As part of the aforementioned multicenter, prospective study, Canani et al[38] evaluated 91 children between the ages of 4 and 36 months with GERD-like symptoms and confirmatory diagnostic studies who were treated with 2 months of either ranitidine or omeprazole. Control subjects were healthy children with no exposure to acid-suppressive medication before study enrollment. During a 4-month follow-up period, the rate of acute gastroenteritis significantly increased in the children exposed to

TABLE 1 Studies Included in Review

Study Author	Type of Study	Age	Location	Medications Investigated	Outcome Assessed	OR (95% CI)
Guillet et al[27]	Retrospective	Neonates	NICU	Ranitidine, famotidine, cimetidine	NEC	1.71 (1.34–2.19), $P < .0001$
Terrin et al[28]	Prospective	Neonates	NICU	Ranitidine	NEC, sepsis, pneumonia, UTI	Infections: 5.5 (2.9–10.4), $P < .001$ NEC: 6.6 (1.7–25), $P = .003$
Beck-Sague et al[29]	Prospective	Neonates	NICU	H_2 antagonists	Bloodstream infection	2.9, $P = .008$
Rojas et al[30]	Prospective	Neonates	NICU	H_2 antagonists	Nosocomial infection	3 (1.1–7.7)
Graham et al[31]	Retrospective	Neonates	NICU	H_2 antagonists or PPI	Gram-negative bacteremia	3.1 (0.96–10.2), $P = .059$
Bianconi et al[32]	Retrospective	Neonates	NICU	Ranitidine	Late-onset sepsis	6.99 (3.78–12.94), $P < .0001$
Elward et al[33]	Prospective	≤18 y	PICU	H_2 antagonists	VAP	$P = .006$
Yildizdas et al[34]	Prospective	Pediatric, age range not specified	PICU	Omeprazole, ranitidine, sucralfate	VAP	$P = .963$
Lopriore et al[35]	Retrospective	Pediatric, age range not specified	PICU	Ranitidine, sucralfate	VAP	–
Sharma et al[36]	Prospective	1 mo–15 y	PICU	Ranitidine	VAP	$P = .025$
Singh-Naz et al[37]	Prospective	Pediatrics, age range not specified	PICU	H_2 antagonists	Nosocomial infection	Univariate $P < .0001$
Canani et al[38]	Prospective	4–36 mo	Pediatric GI centers	Omeprazole and ranitidine	Pneumonia, gastroenteritis	Pneumonia: 6.39 (1.38–29.7), $P < .05$ Gastroenteritis: 3.58 (1.87–6.86), $P = .001$
Orenstein et al[6]	Prospective	28 d–12 mo	Primary care centers	Lansoprazole	Lower respiratory tract infection	$P = .032$
Turco et al[39]	Retrospective	1–18 y	Hospital	PPI, H_2 antagonist	*C difficile* colitis	1.2 (1.04–1.39), $P = .008$

GI, gastroenterology; UTI, urinary tract infection.

acid-suppressive medications compared with the healthy controls (47% vs 20%; $P = .001$). In the logistic regression analysis, children exposed to acid-suppressive medications were still significantly more likely to develop gastroenteritis than the control patients (OR: 3.58 [95% CI: 1.87–6.86]).

Turco et al[39] conducted a single-center, retrospective, case-control study of hospitalized children aged 1 to 18 years with *Clostridium difficile*–associated disease (CDAD). CDAD was defined as protracted diarrhea (>15 days of increased frequency of ≥3 bowel movements in a 24-hour period or decreased consistency of stool), abdominal pain, and positive results on *C difficile* stool toxin. Control subjects were identified as those with similar symptoms but negative results on stool studies for *C difficile* or other pathogens. Sixty-eight cases were identified and matched with 68 controls. The use of PPIs was significantly higher in the *C difficile*–positive group compared with the *C difficile*–negative group (22.1% vs 5.9%; $P = .006$; OR: 4.52 [95% CI: 1.4–14.4]). Although the use of H_2 antagonists was higher in the *C difficile*–positive group, it was not statistically significant. In the multivariate logistic regression analysis, the use of PPIs was significantly associated with CDAD compared with the other variables measured ($P = .008$; OR: 1.2 [95% CI: 1.04–1.39]).

DISCUSSION

Acid-suppressive medications affect infection rate through their impact on gastric acidity, a first-line defense against infections. In normal gastric acidity of pH <4, most pathogens do not survive; however, in a hypochlorhydric or achlorhydric state, pathogens can thrive.[40] This action leads to increased bacterial colonization and pathogenic overgrowth in the stomach and gastrointestinal tract. This theory was supported in a study by Carrion and Egan[41] in which infants fed acidified formula or maternal breast milk achieved lower gastric pH and had significantly lower gastric bacterial colonization. In addition to the effect of acid-suppressive medications on gastric acidity, studies suggest that these agents directly inhibit leukocyte activity and thereby blunt the body's overall immune

response to infection.[42,43] These mechanisms may underlie the increased infections observed in those receiving acid-suppressive medication.

The expansive literature in the adult population has highlighted the negative adverse effects of acid-suppressive medication. In the pediatric literature, this pattern is particularly notable in the NICU and PICU populations in which studies have demonstrated that acid-suppressive medications are associated with increased risk for NEC (OR: 1.71–6.6)[27,28] and sepsis/bacteremia (OR: 2.9–6.99).[29,32] The only area in which results were mixed was VAP, in which 2 studies found a significant association between acid suppression and VAP[33,36] and 2 other studies found no association.[34,35] The 2 studies that showed no association between acid suppression and VAP were largely limited by small sample size and lack of power. Arguments have been made that in a retrospective study, acid-suppressive medications may simply be a marker for sicker infants and children who may inherently have risk factors for infections due to their clinical vulnerability. However, the addition of case-controls to these studies helps to address this issue by comparing critically ill children receiving acid-suppressive medications with other critically ill children not receiving acid-suppressive medications. In the study by Beck-Sague et al,[29] the authors accounted for severity of illness by using a multiple regression analysis and found that H_2 antagonists were independently associated with increased risk of bloodstream infection. Although previously thought in adult studies to be a risk isolated to hospitalized patients with comorbidities, the increased risk for infection has also been observed in healthy adults.[3,16] Likewise, this trend was noted in the study by Canani et al[38] that looked specifically at previously healthy children and the increased risk of pneumonia and gastrointestinal infections on exposure to acid-suppressive medications. Orenstein et al[6] also evaluated infants who had GERD-like symptoms who were primarily managed as outpatients; in this relatively healthy population, the authors observed an increased incidence of serious adverse effects in patients receiving a PPI compared with those who did not (12% vs 2%; $P = .032$). Lower respiratory tract infections were the leading event. This association between acid-suppressive medications and infections, although more extensively studied in sicker populations, is a concern relevant to the general pediatric population.

Published indications for acid-suppressive medications range from suspected GERD to stress ulcer prophylaxis to erosive esophagitis. Often, these indications were not evaluated or well described in the studies reviewed. With the wealth of data in the critical care environment indicating an increased risk of infections in an already vulnerable population, the decision to start acid-suppressive medications in this population should be made with great care. In the otherwise healthy infant or child who has GERD-like symptoms, this decision also needs to be made judiciously. It is important to consider the natural physiologic course of gastroesophageal reflux symptoms. Physiologic reflux is defined as the retrograde movement of gastric contents into the esophagus due to decreased tone of the lower esophageal sphincter, which over time, gains tone and prevents this movement. Uncomplicated gastroesophageal reflux symptoms typically resolve by 1 year of age without intervention.[44] Furthermore, conservative therapy, such as decreased volume and thickened feeds, has been found to decrease GERD symptoms in infants.[45] With the exception of endoscopically confirmed erosive esophagitis, acid-suppressive medications have not been shown to have a beneficial role in GERD, particularly in infants <1 year of age.[10] The majority of cases improve when left to their natural course.

CONCLUSIONS

Given the natural resolution of symptoms and questionable efficacy of H_2 antagonists and PPIs, and with growing evidence indicating increased risk of serious infections, acid-suppressive medications should be used cautiously in infants or children suspected of having GERD. The potential risks should be balanced carefully with the questionable benefits in making this decision.

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