

Early Acid Suppression Therapy Exposure and Fracture in Young Children

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abstract

BACKGROUND: Acid suppression therapy (AST), including proton pump inhibitors (PPIs) and histamine H₂-receptor antagonists (H₂RAs), is frequently prescribed to treat symptomatic gastroesophageal reflux in otherwise healthy infants. PPI use has been associated with increased fracture risk in older adults; 2 preliminary studies in children have conflicting results.

METHODS: A retrospective cohort of children born 2001 to 2013 who were followed for ≥ 2 years was formed. Those with osteogenesis imperfecta, cholestasis, or child maltreatment were excluded. Prescription data were used to identify AST prescription before age 1 year. *International Classification of Diseases, Ninth Revision, Clinical Modification* codes identified fractures after age 1 year. A Cox proportional hazard analysis assessed fracture hazard and was adjusted for sex, prematurity, low birth weight, previous fracture, anti-epileptics, and overweight or obesity.

RESULTS: Of 851 631 included children, 97 286 (11%) were prescribed AST in the first year of life; 7998 (0.9%) children were prescribed PPI, 71 578 (8%) were prescribed H₂RA, and 17 710 (2%) were prescribed both a PPI and H₂RA. Infants prescribed AST had an earlier median first fracture age (3.9 vs 4.5 years). After adjustment, increased fracture hazard was associated with PPI use (21%) and PPI and H₂RA use (30%), but not H₂RA use alone. Longer duration of AST treatment and earlier age of first AST use was associated with increased fracture hazard.

CONCLUSIONS: Infant PPI use alone and together with H₂RAs is associated with an increased childhood fracture hazard, which appears amplified by days of use and earlier initiation of ASTs. Use of AST in infants should be weighed carefully against possible fracture.



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WHAT'S KNOWN ON THIS SUBJECT: Proton pump inhibitors (PPIs) are used frequently in the treatment of symptomatic gastroesophageal reflux. Studies in adults have revealed an association between PPIs and increased fracture risk, but this has not been well studied in infants and children.

WHAT THIS STUDY ADDS: This study included young children without known serious medical conditions prescribed acid suppression therapy during the first year of life, likely for symptomatic treatment of reflux. A positive association was found between PPI use and childhood fracture incidence.

To cite: Malchodi L, Wagner K, Susi A, et al. Early Acid Suppression Therapy Exposure and Fracture in Young Children. *Pediatrics*. 2019;144(1):e20182625

Acid suppressants, including proton pump inhibitors (PPIs) and histamine H₂-receptor antagonists (H₂RAs), are commonly prescribed for the treatment of gastroesophageal reflux (GER) disease, erosive esophagitis, gastric and duodenal ulcers, eosinophilic esophagitis, and *Helicobacter pylori* gastritis. Although these diseases have remained relatively stable over the past decades, the use of PPIs and H₂RAs has increased dramatically, doubling from 2004 to 2008¹ and tripling from 2002 to 2009.² This increase has occurred not only in the adult population but also in pediatrics, with use in infants quadrupling from 1999 to 2003, and doubling from 2004 to 2008.^{3,4} This increase may reflect overtreatment of physiologic newborn reflux and misinterpretation of normal newborn crying.^{5,6} Newborn reflux and crying are normal newborn behaviors, and placebo-controlled trials have revealed that PPIs do not relieve symptoms related to GER in infants.^{7,8}

Although PPIs were initially thought to be safe,⁹ a growing body of research is uncovering several short- and long-term negative effects of PPI therapy.¹⁰ Long-term PPI use in adults has been associated with negative outcomes, including gastric cancers, infection, gastric polyps,¹¹ chronic kidney disease,¹² and overall increased mortality.¹³ In adult studies, PPI use has also been associated with decreased bone mass^{14,15} and an increased rate of fractures.¹⁶ Emerging research is revealing risks with PPI use in the pediatric population as well, with PPI use increasing the risk for gastroenteritis, community-acquired pneumonia, and *Clostridium difficile* infections.^{17,18}

Authors of few studies have looked specifically at bone health¹⁹ in children on PPIs, and the results have been limited and contradictory. A small study of 34 children (ages 5–9

and 12–15 years) revealed that PPIs were not associated with alterations in biochemical indicators of bone turnover.²⁰ A larger study revealed that PPI use was associated with fracture in young adults (ages 18–24 years) but not in children (ages 4–18 years).²¹ In an earlier study, authors exploring the impact of preterm birth on fracture found that first-year PPI use may be associated with an increased fracture rate during the first 5 years of life, although they did not examine the effect of age at time of initiation or duration of exposure.²² Studies also have not been focused on acid suppression therapy (AST) use and fracture risk in otherwise healthy infants despite high prescription rates in this population.²³

In this study, we sought to explore the relationship between AST use in the first year of life and childhood fracture, accounting for duration of exposure and age at initiation. In the study, we hypothesize that prescription use of AST, specifically PPIs, in otherwise healthy infants will be associated with increased incidence of fracture in young children.

METHODS

A retrospective cohort of children born in the Military Healthcare System (MHS) who received continuous MHS care for at least the first 2 and up to 14 years of life was formed. The MHS provides health care to military members, retirees, and dependent family members. Care is provided around the world at military treatment facilities and by civilian providers. Records are maintained for all inpatient and outpatient medical care and outpatient prescription medications.

Children born in the MHS between October 1, 2001, and September 30, 2013, were included. Children with diagnoses that included osteogenesis imperfecta, cholestasis, or child

maltreatment, identified via *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes, were excluded because these conditions independently predispose a child to fractures.²² Cholestasis is oftentimes associated with prolonged parenteral nutrition or chronic liver disease, both of which can increase the risk of metabolic bone disease.²⁴ Birth hospitalizations of ≥ 7 days were used as a surrogate for admission to the NICU, and children with these extended birth hospitalizations were excluded in an attempt to limit the study population to otherwise lower-risk infants.

Data extracted from civilian and military outpatient pharmacy records were used to identify the days supply and refills of all AST prescriptions in the first 5 years of life. Children were classified as having been prescribed either a PPI, an H₂RA, or both if they had ≥ 1 outpatient prescription for these medications during the first year of life. For children who started AST before 1 year of age, prescription data were followed for 5 years to track total length of treatment. These children were compared with children who were not prescribed any AST during the first 5 years of life. Those who initiated AST between the ages of 1 and 5 years were excluded from the primary analysis because later AST prescriptions are uncommon and are more likely related to chronic disease. Children who initiated AST at 12 to 24 months of age were included in a secondary analysis. Pharmacy records were also used to identify any children prescribed an anti-epileptic medication at any point in the study because anti-epileptics have been linked with increased fracture risk.^{25,26}

ICD-9-CM codes were used to identify fractures in the outpatient record that occurred both before and after the age of 1 year by using the Agency for Healthcare Research and Quality

Clinical Classification System category for fractures.²⁷ Any child with a fracture before 1 year of age was categorized as having a previous fracture, because previous fractures can be associated with increased fracture risk.²⁸ Visits for the same fracture type within 6 months were excluded because they were likely follow-up visits and not visits for new fractures. ICD-9-CM codes were used to identify preterm birth (<37 + 0/7 weeks' gestation) and low birth weight (LBW) (weight ≤2500 g) in the inpatient record of any children who were not already excluded for a birth hospitalization of ≥7 days. ICD-9CM codes were also used to identify obesity or overweight status in the outpatient record, because increased BMI has been linked to increased fracture risk and decreased bone mineral density.^{29,30}

Group differences were compared by using the Wilcoxon rank test and χ^2 analysis. A Cox proportional hazard model was used to assess the hazard ratio (HR) of fracture by AST use. An adjusted analysis was used to control for sex, preterm birth, LBW, obesity and/or overweight, anti-epileptics, and history of fracture before 12 months of age. When Schoenfeld residual testing revealed a violation of the proportionality assumption, an interaction with time was added to the model.

Two secondary analyses were used to explore the impact of duration of prescription AST use and age of AST medication initiation. Length of prescription use was divided into quartiles for both H₂RA and PPI groups and for the combination group. Each quartile was compared with controls who were not treated. A Cox proportional hazard model was used to assess the hazard of fracture by days on PPIs, H₂RAs, and both medications; adjusted analyses were used to control for sex, preterm birth, LBW, obesity and/or overweight, anti-epileptics, fracture before 1 year of age, and time. By using 2 models, a sensitivity analysis was performed to explore whether previous fracture affected the relationship between AST and fracture.

Prescription patterns were next grouped by age at initiation. To fully explore age at AST initiation, the final analysis population was expanded to include children who initiated an AST from age 0 to 24 months. Children were classified as being prescribed AST in the first 6 months of life, at 6 to 12 months, and at 12 to 24 months and were compared with controls not prescribed any AST in the first 5 years. An analysis of variance with Tukey comparison was used to examine the impact of AST age of initiation on length of use. A Cox proportional hazard model was used

to assess the relative incidence of fracture by days on PPIs, H₂RAs, and both medications; adjusted analyses were used to control for male sex, preterm birth, LBW, obesity and/or overweight, anti-epileptics, fracture before 1 year of age, and time when indicated.

Stata Intercooled 13 (Stata Corp, College Station, TX) software was used for the statistical analysis. $P < .05$ was considered statistically significant. The study was reviewed and approved by the Uniformed Services University Institutional Review Board.

RESULTS

A total of 1 190 544 infants were born in the MHS between 2002 and 2015. Infants were excluded if they were classified as being at increased risk for fracture because of an extended birth hospitalization of >7 days (40 099; 3.3%), maltreatment (9005; 0.74%), cholestasis (407; 0.03%), or osteogenesis imperfecta (174; 0.01%). Children also were excluded if they received MHS care for <2 years (266 309; 22%) or if they initiated AST after 1 year of age (22 919; 2%). Of the remaining 851 631 infants, 754 345 (89%) did not initiate AST and were study controls, and 97 286 (11%) initiated AST in the first year of life. Of those

TABLE 1 Demographics of Children Prescribed and Not Prescribed AST in the First Year of Life

	All Children (N = 851 631)	AST in the First Year of Life (n = 97 286)	No AST in the First Year of Life (n = 754 345)	P
Median age enrolled (IQR), y	5.8 (3.6–9.1)	5.2 (3.4–8.0)	5.9 (3.6–9.3)	<.001
Total fractures before 1 y of age (per 1000 person-years)	16 050 (16)	2144 (19)	13 906 (16)	<.001
Total fracture after 1 y of age (per 1000 person-years)	124 414 (22)	13 941 (24)	110 473 (21)	<.001
Median age of first fracture (IQR), y	4.4 (2.3–7.3)	3.9 (2.1–6.5)	4.5 (2.3–7.3)	<.001
Sex, n (%)				
Male	435 102 (51.1)	53 764 (55.3)	381 338 (50.7)	<.001
Female	416 529 (48.9)	43 534 (44.7)	372 995 (49.6)	<.001
Preterm birth, n (%)	32 319 (3.8)	6201 (6.4)	26 118 (3.5)	<.001
LBW, n (%)	19 952 (2.3)	3626 (3.7)	16 326 (2.2)	<.001
Anti-epileptic prescription, n (%)	9919 (1.2)	1124 (1.2)	8795 (1.2)	.77
Overweight or obesity, n (%)	49 450 (5.8)	5307 (5.5)	44 143 (5.9)	<.001

IQR, interquartile range.

on AST, 7998 (9%) were prescribed a PPI, 71 578 (73%) were prescribed an H₂RA, and 17 710 (18%) were prescribed both (Supplemental Fig 2). Compared with those not prescribed an acid suppressant in the first 5 years, children who initiated AST by 1 year of age were enrolled and followed in the MHS for a shorter period of time and were less likely to have overweight or obesity. They were more likely to be male, born preterm, and born with LBW. AST was not associated with anti-epileptic prescription medication use (Table 1).

In the unadjusted analysis, the hazard of fracture after 1 year of age was associated with being prescribed a PPI (HR 1.23; 95% CI 1.15–1.32), being prescribed an H₂RA (HR 1.13; 95% CI 1.10–1.15), and being prescribed both an H₂RA and a PPI in the first year of life (HR 1.32; 95% CI 1.26–1.38; Table 2). An increased hazard of fracture was associated with male sex, overweight or obesity, and previous fracture; a decreased fracture hazard was associated with LBW (Table 2). Preterm birth and anti-epileptic medication were not associated with fracture (Table 2). A sensitivity analysis revealed that previous fracture did not affect the association between AST and fracture.

After adjustment for covariates, including time, the association

between AST prescriptions and fracture remained. Fracture hazard increased 23% in children prescribed a PPI (HR 1.23; 95% CI 1.14–1.31) and 31% in children prescribed both an H₂RA and a PPI in the first year of life (HR 1.31; 95% CI 1.25–1.37; Table 2, Fig 1). The adjusted fracture hazard was increased with male sex and previous fracture, was decreased with LBW, and was not associated with overweight or obesity, with anti-epileptic use, or with preterm birth (Table 2). H₂RA initiation in the first year of life was not associated with increased fracture.

An adjusted analysis used to explore effects of prescription length in days suggests that fracture hazard increases with duration of AST exposure. Medication days were divided into quartiles for each medication class. The median prescription length was 60 days for monotherapy with PPIs or H₂RAs and 192 days for combination therapy (Table 3). Children prescribed a PPI for 0 to 30 days had a 19% increased fracture hazard, and those prescribed PPIs for >150 days had a 41% increased fracture hazard (Table 3). Children prescribed a combination of PPIs and H₂RAs for 0 to 120 days had a 17% increased fracture hazard compared with controls with no AST use in the first 5 years of life (Table 3). Use of PPIs and H₂RAs was

associated with increased fracture hazard for medication use for 120 to 192 days (31%), 192 to 338 days (20%), and >338 days (50%; Table 3). Use of H₂RAs alone was associated with increased fracture hazard in those prescribed the medications for 0 to 30 days (14%), 60 to 120 days (16%), and >120 days (22%; Table 3).

Compared with controls with no AST prescriptions before age 5, PPI initiation at 0 to 6 months of life was associated with a 23% increased fracture hazard, PPI initiation at 6 to 12 months was associated with a 21% increase, and PPI initiation at 12 to 24 months was not associated with an increased fracture hazard in the adjusted analysis (Table 4). Children prescribed an H₂RA did not have an increased hazard of fracture regardless of when medication was initiated (Table 4). Fracture hazard was increased in children prescribed both a PPI and an H₂RA, compared with controls with no AST use; PPI and H₂RA initiation at 0 to 6 months was associated with a 32% increase, at 6 to 12 months a 23% increase, and at 12 to 24 months a 38% increase in adjusted analysis (Table 4). Duration of AST exposure decreased with age of initiation ($P < .001$), with the mean length of use differing for all 4 groups.

DISCUSSION

AST medication use during the first year of life was associated with increased fracture hazard in children. The greatest fracture hazard was associated with combination PPI and H₂RA use during the first year of life. PPI use alone was associated with an increased fracture hazard, whereas H₂RA use alone did not significantly impact fracture hazard. Fracture hazard increased with duration of AST use, which suggests a possible dose-dependent response, and with younger age of AST initiation with PPIs, alone or in combination with H₂RAs.

TABLE 2 Unadjusted and Adjusted HRs by AST Use in the First Year of Life

	Unadjusted HR of Fracture (95% CI)	Adjusted HR of Fracture (95% CI)
Male sex	1.08 (1.07–1.10)	1.08 (1.06–1.09)
Preterm birth	0.98 (0.95–1.02)	1.01 (0.97–1.05)
LBW	0.90 (0.86–0.95)	0.90 (0.85–0.94)
Previous fracture	1.85 (1.75–1.96)	3.59 (3.22–4.00) ^a
Anti-epileptic medication	0.98 (0.92–1.04)	0.99 (0.93–1.05)
Overweight or obesity	1.12 (1.09–1.14)	0.99 (0.95–1.04) ^b
PPI use	1.23 (1.15–1.32)	1.23 (1.14–1.31)
H ₂ RA use	1.13 (1.10–1.15)	1.04 (0.99–1.09) ^c
PPI and H ₂ RA use	1.32 (1.26–1.38)	1.31 (1.25–1.37)
Previous fracture and time	—	0.99 (0.99–0.99) ^a
H ₂ RA and time	—	1.00004 (1.00002–1.00006) ^c
Overweight or obesity and time	—	1.00001 (1.00003–1.00007) ^b

—, not applicable.

^a Interaction with time reveals that the impact of previous fracture decreases with time.

^b Interaction with time reveals that the impact of overweight or obesity status on fracture slightly increases with time.

^c Interaction with time reveals that the impact of H₂RA use on fracture slightly increases with time.

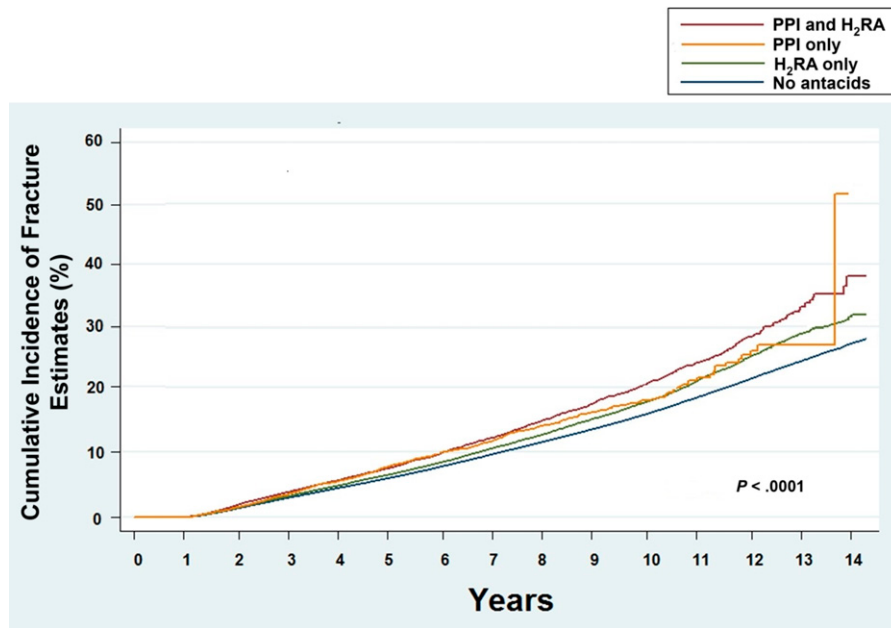


FIGURE 1
Cumulative incidence of fracture estimates by first year of life acid suppression use.

These findings are consistent with adult studies linking AST with increased risk for osteoporotic fracture.^{31,32} Results are also consistent with research linking fracture with early PPI use in infants who were sick and healthy,²² and with findings that PPIs did not increase fracture risk in older children,²¹ because AST initiation after age 1 was not associated with fracture.

Similar to adult studies,³³ fracture hazard increased with prescription duration. The median prescription length for combined therapy (192 days) was considerably longer than

that for PPIs (60 days) or H₂RAs (60 days; Table 3), possibly suggesting that the increased fracture hazard is related to duration of medication use, or perhaps an unidentified confounding disease, rather than a synergistic effect of combined AST.

Fracture hazard increased with younger age of initiation, with children starting at <6 months of age having greater fracture hazard than those starting at 12 to 24 months of age. Results are consistent with the limited previous studies that revealed an increased fracture rate in infants but not in older children.²¹ This may be due to rapid bone turnover that

occurs in the first year of life,³⁴ or this may be because infants who start earlier may continue AST treatment for longer periods of time. Although diagnostic codes indicating prescription rationale could not be linked, results may be related to different indications for medications in older versus younger children. Previous studies infer AST initiation at age ≤6 months is for treatment of symptoms of GER or GER disease,³⁵ which is difficult to diagnose in infants, and that the majority of children outgrow symptoms by age 1.

The exact mechanism linking AST with bone health is unclear; however,

TABLE 3 Adjusted Hazard of Fracture Associated With AST Started Before Age 1 by Duration of Exposure

PPIs (n = 7998)		H ₂ RAs (n = 71 578)		Both H ₂ RAs and PPIs (n = 17 710)	
Days on Medication	Adjusted HR (95% CI)	Days on Medication	Adjusted HR (95% CI)	Days on Medication	Adjusted HR (95% CI)
0–30	1.19 (1.11–1.29)	0–30	1.14 (1.09–1.18)	0–120	1.17 (1.06–1.29)
30–60	1.20 (1.09–1.33)	30–60	0.99 (0.90–1.08) ^a	120–192	1.31 (1.18–1.47)
60–150	1.23 (1.13–1.33)	60–120	1.16 (1.11–1.21)	192–338	1.20 (1.08–1.32)
>150	1.41 (1.32–1.52) ^b	>120	1.22 (1.17–1.27) ^c	>338	1.50 (1.37–1.65) ^d

Models were adjusted for male sex, preterm birth, LBW, anti-epileptic medication use, overweight or obesity, previous fracture, and time.

^a Interaction with time reveals that the impact of H₂RA use on fracture slightly increases with time.

^b Differed significantly from 0–30, 30–60, and 60–150 d.

^c Differed significantly from 0–30 and 30–60 d.

^d Differed significantly from 0–120 and 192–338 d.

TABLE 4 Adjusted Hazard of Childhood Fracture Associated With Early AST, Stratified by Age of Prescription Initiation

	Initiated in First 6 mo (n = 84 845)		Initiated at Ages 6–12 mo (n = 12 441)		Initiated at Ages 12–24 mo (n = 8390)	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Male sex	1.08 (1.07–1.09)	1.08 (1.06–1.09)	1.08 (1.07–1.10)	1.08 (1.06–1.09)	1.08 (1.07–1.10)	1.08 (1.07–1.10)
Preterm birth	0.97 (0.94–1.01)	0.99 (0.96–1.04)	0.98 (0.95–1.02)	1.03 (0.98–1.07)	0.98 (0.94–1.02)	1.02 (0.97–1.06)
LBW	0.90 (0.86–0.94)	0.90 (0.85–0.95)	0.89 (0.85–0.94)	0.89 (0.84–0.94)	0.89 (0.85–0.94)	0.89 (0.84–0.94)
Previous fracture	1.85 (1.74–1.96)	3.57 (3.20–3.98) ^a	1.85 (1.74–1.96)	3.52 (3.14–3.95) ^a	1.85 (1.74–1.97)	3.50 (3.13–3.93) ^a
Overweight or obesity	1.12 (1.09–1.14)	0.99 (0.94–1.04) ^b	1.12 (1.09–1.15)	0.99 (0.94–1.05) ^b	1.12 (1.09–1.15)	0.99 (0.94–1.04) ^b
Anti-epileptics	0.98 (0.92–1.04)	0.98 (0.92–1.05)	0.98 (0.92–1.05)	0.98 (0.92–1.05)	0.98 (0.92–1.05)	0.98 (0.92–1.05)
PPI use	1.24 (1.14–1.34)	1.23 (1.14–1.33)	1.21 (1.05–1.40)	1.21 (1.05–1.39)	1.13 (0.98–1.30)	1.06 (0.91–1.24)
H ₂ RA use	1.12 (1.09–1.15)	1.04 (0.99–1.10) ^c	1.15 (1.08–1.22)	1.04 (0.92–1.17) ^c	1.10 (1.01–1.19)	0.91 (0.75–1.11)
PPI and H ₂ RA use	1.33 (1.27–1.39)	1.32 (1.26–1.38)	1.24 (1.08–1.42)	1.23 (1.07–1.41)	1.42 (1.20–1.68)	1.38 (1.16–1.65)
Previous fracture and time	—	0.9996 (0.9996–0.9997) ^a	—	0.9996 (0.9996–0.9997) ^a	—	0.9996 (0.9996–0.9997) ^a
H ₂ RA and time	—	1.00004 (1.00002–1.00007) ^c	—	—	—	—
Overweight or obesity and time	—	1.00005 (1.00003–1.00007) ^b	—	1.00005 (1.00003–1.00007) ^b	—	1.00006 (1.00004–1.00008) ^b

—, not applicable.

^a Interaction with time reveals that the impact of previous fracture decreases with time.

^b Interaction with time reveals that the impact of overweight or obesity on fracture increases slightly with time.

^c Interaction with time reveals that the impact of H₂RA use on fracture increases slightly with time.

biologically plausible hypotheses exist. It was previously postulated that PPIs could impair calcium absorption because of their effect on gastric acid secretion,³⁶ leading to compensatory hyperparathyroidism and increased osteoclast activity.³⁷ Adult studies, however, revealed no significant difference in bone density or blood calcium levels in patients on long-term PPI therapy versus none.^{38,39} Another theory is that PPIs change osteoclast activity and viability.⁴⁰ Osteoclasts have a proton pump on their surface, which, if inhibited, could lead to osteoclast dysfunction and unopposed osteoblast activity resulting in a disorganized and potentially more fragile bone matrix.² One study of pantoprazole on human osteoclasts in vitro revealed that exposed osteoclasts had significantly lower viability and activity, although no change was seen in osteoclast-specific gene expression.⁴¹

The effect of H₂RAs on bone development has been less studied compared with that of PPIs and is less strongly associated with fracture. Older adult users of H₂RAs showed decreased bone mineral density on dual-energy radiograph absorptiometry scans, but this was seen only in those not taking calcium supplements.³² One adult study revealed no association between H₂RAs and fracture,⁴² and another revealed reduced fractures in adults on combination H₂RA and PPI therapy, compared with PPI use alone.⁴³ The authors of these studies, however, explored the effect of AST on the adult bone, which may react differently to PPI and H₂RA exposure than the rapidly growing and remodeling bone of young children.

Although an association between AST use in infancy and increased fracture risk was found, findings do not explore fracture patterns or mechanism of injury. Children with ICD-9-CM codes for child maltreatment were excluded; however, the incidence of recorded

maltreatment in this study population was low, likely indicating that all children who were maltreated were not excluded. Only more severe maltreatment is regularly coded in the electronic health record. In addition, infant victims of maltreatment often present with symptoms that include fussiness and GER or vomiting, which could result in an AST prescription.^{44,45}

Study findings do not establish a causal relationship between PPI exposure and fracture. Practitioners should continue to take appropriate actions when they evaluate children with histories, injuries, or fracture patterns that cause concern for potential abuse, regardless of AST exposure.

This study is additionally limited by use of prescriptions as a proxy for taking medication; researchers were unable to assess if children consistently used the medication for the full prescription period and were unable to account for different dosing methods or prescribing patterns over time. In the study, we also excluded appointments for the same type of fracture within 6 months as follow-up appointments; this determination may have resulted in misclassification

of some new cases of fracture as follow-up. Although factors most known to be associated with fracture in young children were accounted for, other potential confounders, including socioeconomic status, geographic region, breastfeeding status, use of other medications, or comorbid conditions besides those in this study's exclusion criteria, were not captured or included. Finally, the use of such a large sample may have overpowered our analyses.

This study has multiple strengths, including a large population and the ability to identify and exclude children with conditions that place them at highest risk for fractures. The MHS provides free health care and free or low-cost prescriptions, reducing access-to-care and ascertainment bias. Finally, in this study, we examined the impact of AST prescribed during infancy on fracture risk over a longer time period (compared with that in previously reported studies).

CONCLUSIONS

AST used in the first year of life, especially PPIs, are associated with increased fracture hazard

in children. Results should not be interpreted to suggest that PPIs or H₂RAs alone explain fractures, which is important in suspected cases of nonaccidental trauma. Results indicate longer AST use and earlier initiation may increase fracture hazard. Practitioners should be aware of the potential for fracture when considering treatment with AST versus lifestyle changes and watchful waiting. If AST use is necessary, providers should limit prescriptions to a single drug and limit their duration when possible.

ABBREVIATIONS

AST: acid suppression therapy

GER: gastroesophageal reflux

H₂RA: histamine H₂-receptor antagonist

HR: hazard ratio

ICD-9-CM: *International Classification of Diseases, Ninth Revision, Clinical Modification*

LBW: low birth weight

MHS: Military Healthcare System

PPI: proton pump inhibitor

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DOI: <https://doi.org/10.1542/peds.2018-2625>

Accepted for publication Mar 29, 2019

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2019-0909.

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