The Impact of the American Academy of Pediatrics Brief Resolved Unexplained Event Guidelines on Gastrointestinal Testing and Prescribing Practices

Daniel R. Duncan, MD, MPH[1], Amanda S. Growdon, MD[2], Enju Liu, PhD[3], Kara Larson, MS, CCC-SLP[1], Madeline Gonzalez, BS[4], Kerri Norris, BS[4], and Rachel L. Rosen, MD, MPH[1]

Objectives To determine if hospitalization, testing, diagnosis, and management of suspected gastroesophageal reflux, and follow-up visits decreased since introduction of American Academy of Pediatrics guidelines for brief resolved unexplained events (BRUEs).

Study design We performed a retrospective cohort study of infants with BRUE evaluated at Boston Children's Hospital in the year before and after guideline implementation to determine if practice patterns have changed. Outcomes included hospitalization rates, frequency of swallow assessments, other diagnostic testing, and reflux diagnoses, cost of care, and number of repeat visits. Groups were compared based on whether they presented before or after guideline implementation.

Results In total, 359 subjects (186 pre-, 173 post-guidelines) were identified. There were no significant differences in practice patterns or outcomes before or after guideline implementation. Subjects had mean age 2.53 ± 0.15 months, and 80% were hospitalized for 2.49 ± 0.26 days. Each subject had 2.47 diagnostic tests performed, and 89% were noncontributory. Despite only 13% having videofluoroscopic swallow study performed, 72% showed aspiration/penetration. No subject had gastroesophageal reflux testing, yet reflux was implicated as the cause for admission in 40% of subjects, resulting in increased odds of discharge on acid suppressing medications (OR 2.88, 95% CI 1.68-4.92, $P = .0001$). In follow-up, 28% of subjects had repeat hospitalizations or emergency department visits for persistent symptoms.

Conclusions Infants with BRUE continue to undergo low-yield diagnostic testing and after admission remain symptomatic and frequently re-present to medical care. Swallow testing remains infrequent despite its high-yield, reflux continues to be implicated and children are still being discharged on acid suppression despite lack of efficacy. *(J Pediatr 2019;211:112-9)*.

Brief resolved unexplained events (BRUEs) are frightening episodes characterized by choking, pallor, cyanosis, and limpness in previously healthy infants. Numerous studies have attempted to outline appropriate management strategies, but a major limitation of this research is that the definition remains subjective and includes a heterogeneous patient population.[1,2] Previously known as apparent life-threatening events, they were re-conceptualized as BRUE in 2016 American Academy of Pediatrics (AAP) clinical practice guidelines; with this reconceptualization a management algorithm was proposed, recommending limited testing based on history and physical examination.[3-6]

Although gastroesophageal reflux disease (GERD) is frequently implicated in these patients, pediatric gastroenterologists are often not involved in the initial diagnosis or management of patients with BRUE but are commonly involved in their follow-up care, which often includes un-doing or reversing the diagnosis of GERD and changing the management plan in these patients who typically have recurrent symptoms.[1,2,7-9] In fact, gastroenterologists are much more likely to diagnose swallowing dysfunction, which has been shown to be the most common modifiable diagnosis that can improve outcomes in infants with BRUE.[10,11]

It is understandable that these patients are misdiagnosed with GERD because the symptoms of swallowing dysfunction are indistinguishable from GERD and

AAP	American Academy of Pediatrics
BRUE	Brief resolved unexplained event
GERD	Gastroesophageal reflux disease
H2RA	H2 receptor antagonist
HR	Hazard ratio
PPI	Proton pump inhibitor
VFSS	Videofluoroscopic swallow study

From the [1]Aerodigestive Center, Division of Gastroenterology, Hepatology, and Nutrition, Boston Children's Hospital, Boston, MA; [2]Division of General Pediatrics, Boston Children's Hospital, Boston, MA; [3]Institutional Centers for Clinical and Translational Research, Boston Children's Hospital, Boston, MA; and [4]Department of Reimbursement and Decision Support, Boston Children's Hospital, Boston, MA

Supported by The Translational Research Program at Boston Children's Hospital, National Institutes of Health R01 DK097112-01, and National Institutes of Health T32 DK007477-33. The authors declare no conflicts of interest.

Portions of this study were presented in part at Digestive Diseases Week, June 2-5, 2018, Washington, DC; and NASPGHAN, October 24-27, 2018, Hollywood, Florida.

https://doi.org/10.1016/j.jpeds.2019.04.007

include gagging, choking, coughing, and blue spells.[12,13] Furthermore, because 80% of aspiration is silent in infants, there are no historical clues to make the diagnosis.[8,9] In fact, in infants undergoing swallowing assessments for BRUE using videofluoroscopic swallow study (VFSS), 73% had evidence of aspiration during swallowing, making this is the highest yield test of any performed in infants with BRUE.[10] Unfortunately, the AAP BRUE guideline only recommends an assessment of feeding difficulties if suggested by the patient's presentation, but we now know this is impossible because of the high rate of silent aspiration.[4] Making the incorrect diagnosis of GERD has significant implications; it can result in inappropriate treatment with acid suppression medications, which actually can worsen outcomes and delays the correct diagnosis in infants who are very symptomatic.[10,14]

Therefore, the goal of this study was to determine if publication of the AAP BRUE algorithm resulted in a reduction in diagnostic testing and hospitalizations; an increased incorporation of swallow testing in evaluation of these patients; a decrease in the number diagnoses of suspected GERD and acid suppression use; and a reduction in readmissions and emergency department (ED) visits.

Methods

We reviewed records of infants with BRUE evaluated at Boston Children's Hospital between June 2015 and May 2016 (pre-algorithm) and June 2016 and May 2017 (post-algorithm). We selected these 2 periods to compare differences in diagnostic evaluations and outcomes before and after guideline publication and subsequent implementation. Subjects were identified with Informatics for Integrating Biology and the Bedside (i2b2, Partners Healthcare Systems, Boston, Massachusetts) software using *International Classification of Diseases* codes for apparent life threatening event (R68.13), cyanosis (R23.0), and apnea (R06.81) for any child under 1 year of age.[15] Charts were reviewed to confirm that each presentation was consistent with the BRUE definition; any subjects not meeting the definition were excluded prior to completing in-depth chart review.[4] Subjects with significant medical diagnoses prior to BRUE presentation (eg, seizure disorder, cyanotic heart disease, metabolic disorder) were excluded.

Charts were reviewed to determine baseline characteristics, prior visits for similar symptoms, hospitalization rates at presentation, length of stay for initial presentation, frequency of diagnostic testing and diagnostic yield of tests, treatment with acid suppressing medications, including H2 receptor antagonists (H2RA), and proton pump inhibitors (PPIs), based on prescriptions in charts and medical record documentation of home medications, whether discharge summaries or consultant documentation included reference to or discharge diagnosis of GERD, and number of repeat visits for similar symptoms (eg, choking, color changes, change in tone). To tally repeat visits, we included hospital admissions, emergency department (ED) visits, combined hospital admission and ED (because there were some subjects that came to the ED for persistent symptoms and were not admitted but were admitted at later points for persistent or recurrent symptoms), and clinic visits at Boston Children's Hospital in the 6 months following BRUE. This 6-month follow-up period was selected because most subjects would have been beyond the risk of repeat BRUE at that point. Reasons for repeat visits were identified based on chart reviews, discharge diagnoses, and billing codes. Diagnostic tests were considered contributory if the results could provide an explanation for BRUE symptoms.

Swallow evaluations were reviewed to determine if subjects had VFSS or clinical feeding evaluation. VFSS were considered abnormal if there was evidence of aspiration or laryngeal penetration for any consistency. Laryngeal penetration was considered abnormal because these patients have similar outcomes to patients with overt aspiration and respond to thickening.[16-18] Clinical feeding evaluations were performed by speech language pathologists; VFSS were performed as previously described.[8,19-22]

Hospital billing records were reviewed to determine total charges for BRUE visits and follow-up charges for the 6 months following BRUE hospitalization. Outliers, with charges totaling over $1 million, were excluded from this analysis.

Proportions were compared with the Fisher exact test and continuous outcomes with *t* tests. VFSS and clinical feeding evaluation were compared using the McNemar test. Cox proportional hazards models were used to estimate hazard ratios (HRs) and corresponding 95% CIs for time to repeat admission/ED visit. Covariates adjusted for in the model included age at BRUE, sex, premature status at birth, and total number of diagnostic tests performed during BRUE hospitalizations. All statistical tests were 2-sided with P value of $<.05$ considered statistically significant. All data were analyzed using SPSS Statistics v 23 and SAS v 9.4 (SAS Institute, Cary, North Carolina).

The present study was approved by the Institutional Review Board at Boston Children's Hospital.

Results

Subject Characteristics

Table I shows presenting characteristics; there were no differences in the periods before and after the guidelines. **Figure 1** (available at www.jpeds.com) is a flow diagram of the study population. Patient demographics showing the high proportion of local patients are shown in **Figure 2** (available at www.jpeds.com). BRUE admissions were evenly distributed throughout all seasons of the year.

Length of stay and proportion of patients hospitalized did not change significantly after guideline publication, as shown in **Table I**. Premature subjects had longer length of stay compared with full term subjects (3.73 ± 0.68 vs 2.12 ± 0.26, $P = .028$). There were 2 patient deaths in the second year (0.6% of total cohort), one from unexplained causes during follow-up and another from cerebral hemorrhage related to suspected neurometabolic disorder diagnosed during BRUE hospitalization.

Table I. Subject characteristics

Subject characteristics	Pre-algorithm (n = 186)	Post-algorithm (n = 173)	*P* value
Age (mo)	2.36 ± 0.19*	2.70 ± 0.23	.25
Premature	49 (26)	33 (19)	.10
Gestational age (wk)	32.88 ± 0.46	33.78 ± 0.44	.16
Female sex	108 (58)	95 (55)	.60
Breastfed	83 (45)	88 (51)	.13
Prior visits	38 (20)	24 (14)	.38
Prior ED	11 (6)	7 (4)	.48
Prior clinic for symptoms	27 (15)	17 (10)	.20
Admitted to hospital	153 (82)	135 (78)	.35
Not admitted	33 (18)	38 (22)	.35
Length of stay (d)	2.65 ± 0.40	2.31 ± 0.32	.50

Subject characteristics for the cohort, showing no difference between year the before and the year after BRUE guidelines, including similar proportion with prior visits, admission rates, and lengths of stay.
*Mean ± SE or n (%).

Subsequent Visits

Table II shows subsequent visits after the initial admission; 28% of subjects were either readmitted or seen back in the ED (without hospital admission) for similar symptoms. Repeat ED and hospital admission diagnoses that were found to increase in the second year were feeding difficulties (1% vs 9%, $P = .007$), respiratory symptoms (14% vs 35%, $P = .001$), and vomiting (3% vs 19%, $P = .0002$). Premature infants were more likely to have subsequent readmissions compared with full term infants; 23% of preterm infants were readmitted vs 13% of term infants, $P = .035$.

Swallow Evaluations

Table III (available at www.jpeds.com) shows results of clinical feeding evaluations performed during and after the hospitalization. In a comparison between speech language pathologist recommendations before and after the algorithm, fewer subjects were sent for confirmatory VFSS in the second year despite the high rates of silent aspiration which limits the sensitivity of the clinical feeding evaluation. There was poor correlation between clinical feeding evaluation and VFSS results for subjects that had both evaluations, with 33% of subjects with reassuring clinical feeding evaluation ultimately found to have aspiration/penetration on VFSS ($P < .0005$).

Table II. Subsequent visits

Subsequent visits	Pre-algorithm (n = 186)	Post-algorithm (n = 173)	*P* value
Repeat admission	33 (18)*	23 (13)	.31
Repeat ED without admit	32 (17)	25 (15)	.56
Repeat admit or ED	58 (31)	41 (24)	.13
1+ Clinic visits for symptoms	82 (44)	66 (38)	.28
2+ Clinic visits for symptoms	60 (32)	46 (27)	.25
Mean admits	0.26 ± 0.06	0.20 ± 0.05	.40
Admit nights	4.97 ± 1.47	3.26 ± 0.55	.28
Mean ED visits	0.30 ± 0.06	0.20 ± 0.04	.17
Mean clinic visits	2.2 ± 0.31	1.35 ± 0.21	.02

Subsequent visits for symptoms similar to BRUE during follow-up period, showing no significant change in subsequent admissions, admission nights, or repeat ED visits between the 2 years.
*n (%).

Table IV. Videofluoroscopic swallow study results

VFSS results	Pre-algorithm (n = 186)	Post-algorithm (n = 173)	*P* value
VFSS performed Ever	44/186 (24)*	35/173 (20)	.45
During admission	24/186 (13)	12/173 (7)	.12
After admission	20/186 (11)	23/173 (13)	.62
Mo from admit to VFSS	2.23 ± 0.72	2.72 ± 0.56	.60
2+ admits prior to VFSS	7/44 (16)	4/35 (11)	.55
VFSS results Normal	15/44 (34)	17/35 (49)	.25
Aspiration	15/44 (34)	7/35 (20)	.13
Silent	15/15 (100)	7/7 (100)	1.0
Penetration	14/44 (32)	11/35 (31)	1.0
Change in management	27/44 (61)	17/35 (49)	.36
Change in flow rate	7/27 (26)	5/17 (29)	.15
Thickening	14/27 (52)	12/17 (71)	1.0
Made NPO	6/27 (22)	0/17 (0)	1.0

NPO, nothing by mouth.
Proportion with VFSS testing, findings on VFSS, and change in management based on VFSS results. All subjects with aspiration on VFSS had silent aspiration.
*Mean ± SE or n (%).

VFSS results are in Table IV. Specific consistencies recommended as a result of VFSS are shown in Table V (available at www.jpeds.com). Only 13% of subjects had VFSS performed during their admission, and 72% of these studies showed aspiration/penetration. Furthermore, 42% of subjects that underwent VFSS were breastfed and 58% were bottle fed. Of the breastfed infants, 58% of VFSS were abnormal. Of the patients that were bottle fed, 61% had an abnormal VFSS.

In the cohort overall, 15% of subjects had 2 or more ED visits or hospitalizations for BRUE before undergoing a VFSS. One hundred percent of patients with aspiration on VFSS had silent aspiration. At the time of the BRUE admission, premature infants were more likely to undergo clinical feeding evaluations and VFSS and also more likely to have aspiration/penetration on VFSS, compared with full term infants (74% vs 50% abnormal, $P = .038$).

Figure 1 shows VFSS testing rates and repeat visits. Of the subjects that were not admitted or did not have VFSS during their BRUE admission, 15% went on to have clinical feeding evaluation and/or VFSS in follow-up because of persistent symptoms. Subjects that had VFSS during their initial admission had fewer combined ED visits and admissions in the 6 months following the index admission compared with subjects that had VFSS later (0.46 ± 0.15 vs 1.29 ± 0.30, $P = .017$).

One-half of subjects were breastfed, and 30% of these subjects had lactation evaluation while hospitalized. Of the lactation consultations, 31% resulted in change in management, including change in position/latch adjustments to decrease rapid flow. There was no significant difference in repeat hospitalization rates between breastfed and bottle-fed infants in either year ($P > .29$).

Other Diagnostic Testing

Diagnostic testing remained common after the guidelines, as in Table VI. A mean of 2.47 ± 0.11 tests were performed for each subject with 45% of patients having 3 or more tests. Eighty-nine percent of tests yielded negative,

Table VI. Diagnostic testing rates and yields

Acid suppression status	Pre-algorithm (n = 186)	Post-algorithm (n = 173)	*P* value
Mean diagnostic tests performed	2.31 ± 0.16*	2.64 ± 0.17	.15
Mean test contribution rate	0.12 ± 0.02	0.11 ± 0.02	.68
EKG			
Performed	105 (57)	111 (64)	.16
Contributory	0 (0)	5 (5)	.06
Lab testing			
Performed	59 (32)	71 (41)	.08
Contributory	3 (5)	2 (3)	.66
Chest radiograph			
Performed	67 (36)	59 (34)	.74
Contributory	3 (5)	6 (10)	.30
Infectious testing			
Performed	40 (22)	45 (26)	.32
Contributory	5 (13)	9 (20)	.39
EEG			
Performed	24 (13)	30 (17)	.30
Contributory	2 (8)	7 (23)	.27
Echocardiogram			
Performed	20 (11)	27 (16)	.21
Contributory	1 (5)	1 (4)	1.00
VFSS			
Performed	24 (13)	12 (7)	.08
Contributory	20 (83)	6 (50)	.05
Flexible laryngoscopy			
Performed	20 (11)	15 (9)	.59
Contributory	4 (20)	2 (13)	1.00
Head ultrasound			
Performed	10 (5)	16 (9)	.22
Contributory	1 (10)	1 (6)	1.00
Abdominal radiograph			
Performed	12 (7)	10 (6)	.83
Contributory	0 (0)	0 (0)	1.00
Brain MRI			
Performed	6 (3)	15 (9)	.04
Contributory	2 (33)	3 (20)	1.00
Sleep study			
Performed	8 (4)	6 (4)	.79
Contributory	1 (13)	1 (17)	.58
Abdominal ultrasound			
Performed	5 (3)	8 (5)	.40
Contributory	1 (20)	1 (13)	1.00
Head CT			
Performed	4 (2)	6 (4)	.53
Contributory	1 (25)	2 (33)	1.00
Upper GI			
Performed	3 (2)	5 (3)	.49
Contributory	0 (0)	0 (0)	.44

EKG, Electrocardiogram; *EEG*, Electroencephalogram; *CT*, Computed Tomography; *MRI*, Magnetic Resonance Imaging; *GI*, gastrointestinal.
All testing performed during BRUE evaluation, including proportion that had each test and proportion for which each test contributed to evaluation. EKG was most commonly performed but low-yield while VFSS was infrequently performed but highest-yield.
*Mean ± SE or n (%).

noncontributory results. VFSS was the highest yield test ordered with 72% of results abnormal. There was no significant difference in diagnostic testing rate or overall yield of diagnostic tests for premature infants. There was no difference in diagnostic yield of any individual diagnostic test (all $P > .221$).

Hospital Charges

Combined charges and charge breakdown for all BRUE presentations are shown in **Figure 2**. This value increased from the first year to the second, from $2 198 121 to $2 588 703, an increase of 18% in charges while admissions actually decreased by 7%. Mean charges were $12 144 per patient for the year before and $15 409 per patient for the year after guidelines. Follow-up charges for the 6-months following BRUE totaled $2.4 million. This included $7834 per patient before and $5268 per patient after the guidelines ($P = .174$). Postdischarge charges consisted largely of room and board for repeat admissions (42%), diagnostic testing (22%), and ED care for subsequent visits (11%).

Reflux Attribution and Treatment

No patient in either year had reflux testing by pH/impedance. Only 5% of subjects had a gastroenterology consult. Despite lack of gastroenterologist involvement, 33% of clinical feeding evaluations, 17% of lactation consultants, and 40% of discharge documents attributed the event to reflux. The proportion of patients discharged on any acid suppression decreased from 24% to 15% ($P = .046$) from the first to the second year, but the proportion of patients treated during and after admission (ie, ever treated) with any acid suppression following BRUE admission (ie, started by pediatricians or specialists) remained constant at 31%. Eight percent were discharged on PPI in both years ($P = .84$); 18% were discharged on H2RA in the year before the guidelines, compared with 8% discharged on H2RA in the year after the guidelines ($P = .005$). Fifteen percent were ever treated with PPI in both years ($P = .38$), and 24% were ever treated with H2RA in both years ($P = .62$). Subjects were more likely to have been discharged on acid suppression if the event was attributed to reflux by any of the consultants who saw the patient (OR 2.88, 95% CI 1.68-4.92, $P = .0001$), as shown in **Figure 3**. Subjects were also more likely to ever be treated with acid suppression following BRUE if the event was attributed to reflux (OR 2.43, 95% CI 1.53-3.83, $P = .0002$). Premature subjects were significantly more likely to be placed on acid suppression medications compared with full term subjects (32% vs 16% at discharge with $P = .002$, and 45% vs 27% ever following BRUE, $P = .003$).

Table VII (available at www.jpeds.com) shows results of Cox proportional hazards analysis comparing time with repeat ED visit and/or hospitalization for subjects that were or were not discharged on or ever treated with acid suppression, showing no improvement in outcomes for infants treated with acid suppression (HR 0.76, 95% CI 0.47-1.25, $P = .28$ for subjects discharged on acid suppression and HR 1.42, 95% CI 0.96-2.11, $P = .08$ for subjects ever on acid suppression). **Figure 4** (available at www.jpeds.com) shows Kaplan-Meier curves showing no improvement in risk of subsequent admission or ED visit for subjects discharged on acid suppression or ever treated with acid suppression.

Discussion

We compared management and outcomes for patients with BRUE to determine if practice patterns have changed and outcomes have improved since introduction of the

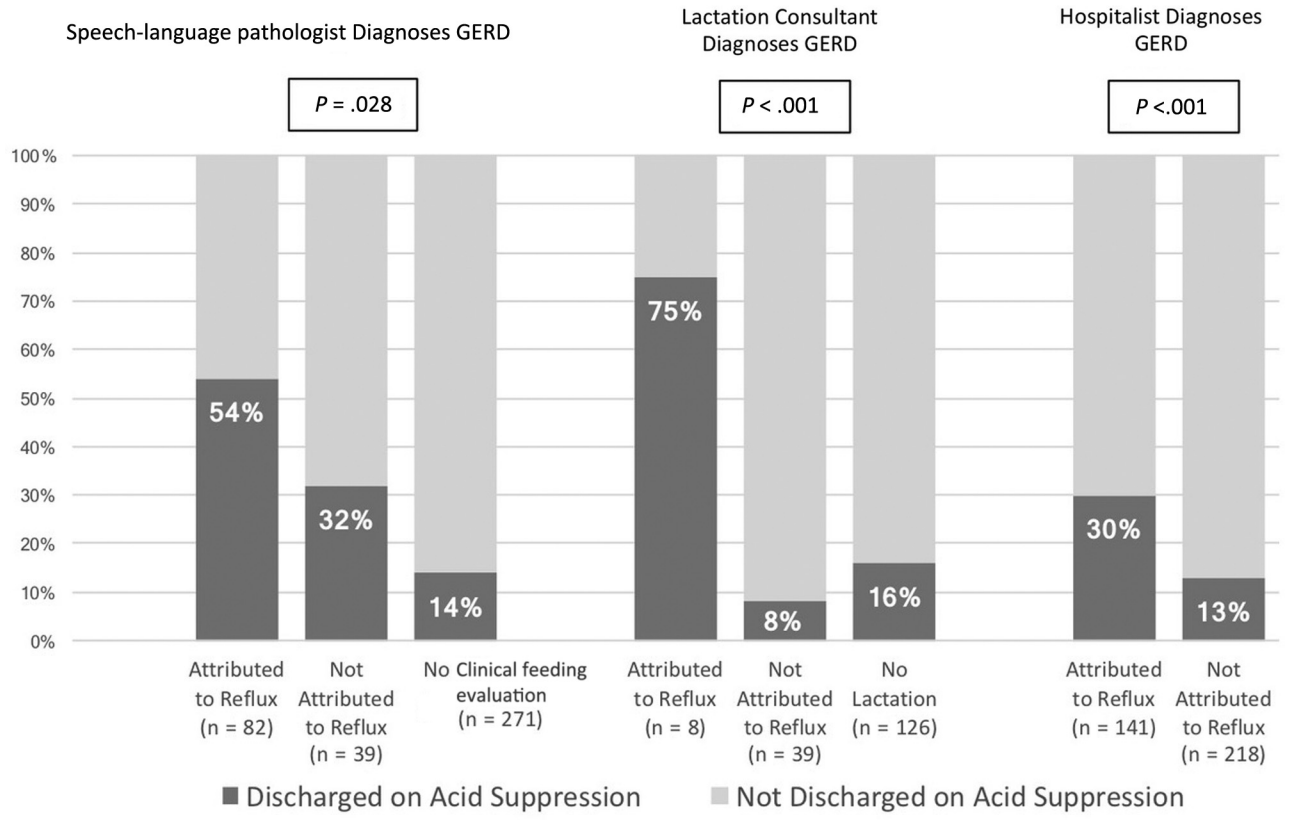

Figure 3. Proportion of subjects discharged on acid suppression varies by attribution to reflux. Association between whether BRUE was attributed to reflux and whether subjects were discharged on acid suppression, showing that attribution to reflux by speech language pathologist in clinical feeding evaluation, lactation consultant, or hospitalist team in discharge summary are all associated with increased odds of discharge on acid suppression.

AAP guidelines, and if swallowing dysfunction remains common in these patients. Our results suggest 5 key findings: (1) BRUE admissions remain common; (2) BRUE management continues to be expensive and involves a great deal of low-yield testing; (3) the highest-yield test, VFSS, remains underutilized; (4) the diagnosis of GERD is often made, resulting in prescription of ineffective medications during and after admission based on this diagnosis; and (5) patients remain symptomatic after discharge and frequently represent to care. Our results suggest that practice patterns and outcomes have changed very little in the year after publication of the BRUE algorithm. Management of these patients remains expensive. It is important to acknowledge that many providers continue to attribute these events to reflux, but our results suggest this approach might not only be unhelpful, this misattribution might also be harmful. Misdiagnosis can result in the inappropriate prescription of acid suppression and a failure to order a videofluoroscopic study to assess swallow function.

Despite the prevalence of low-yield testing, VFSS remains underutilized in this population despite its high yield in this study and prior studies showing that aspiration is silent and cannot be detected by history or observed feedings.[8-10] A major advance resulting from close collaborations and research emanating from aerodigestive centers is the recognition that oropharyngeal dysphagia with aspiration puts patients at risk for symptoms such as BRUE.[8,10,11,23-26] This recognition of swallowing dysfunction is critical in all patients with BRUE, and in infants in general, as the prevalence of oropharyngeal dysphagia is increasing in the pediatric population, which may be due to increased survival of premature infants and children with chronic disease.[12,27,28] It may also be because of increased recognition of swallowing difficulties since many of these patients were previously misdiagnosed as having GERD.

Considering all of the other low-yield testing patients with BRUE undergo, performance of the VFSS as the first-line study for these infants could result in cost savings. Based on $5231 in mean daily charges for subjects that had VFSS during admission, if VFSS were performed on the first day of the admission instead of the fourth, an estimated $24 010 may have been saved.

Providers might not obtain swallow studies for patients presenting with BRUE for a variety of reasons, including concerns about radiation exposure, concerns for whether mild abnormalities on VFSS warrant intervention, and the

assumption that history and observed feedings can reliably replace fluoroscopic studies. First, we and others have shown that radiation exposure is relatively low with VFSS and significantly less than upper gastrointestinal series and less than many of the tests the infants are undergoing as part of the BRUE evaluation.[8,29] Second, regarding the question of if swallowing abnormalities (aspiration/penetration) are normal, we have also previously shown that infants with even mild abnormalities of swallow function (ie, isolated laryngeal penetration), have improved outcomes including a reduction in hospitalizations for respiratory exacerbations after treatment with feeding interventions.[18] Finally, we and others have consistently shown that aspiration cannot be diagnosed by observed clinical feeding or by symptoms; 100% of patients in the present study who had aspiration on VFSS had silent aspiration, suggesting that neither clinical feeding evaluation nor characterization of symptoms during feedings could have further stratified the risk of aspiration among patients with BRUE or predicted the VFSS results. In addition, 33% of subjects with a reassuring clinical feeding evaluation were ultimately found to have aspiration/penetration on VFSS, confirming that the assumption that VFSS might be unnecessary is incorrect.[8,29]

The symptoms of oropharyngeal dysphagia overlap completely with gastroesophageal reflux and our study shows that GERD continues to be inappropriately diagnosed in BRUE, despite multiple prior studies showing that GERD is not a causative factor in these patients.[4,30-35] Diagnosing GERD has significant implications and, as shown in this study, a variety of providers are making this diagnosis. Patients diagnosed with GERD in this study were twice as likely to have been discharged on or ever be treated with acid suppression if the BRUE was attributed to reflux. This is an important reminder that labeling a child with this diagnosis can be harmful, elegantly illustrated by reports that just the use of the GERD diagnosis made parents interested in reflux medicines even after being told they would likely be ineffective.[36] It is critical that providers and consultants avoid inappropriately labeling patients with GERD given implications on acid suppression prescribing. Not only are these medications unhelpful because the majority of infant reflux is nonacidic, many adverse effects have been associated with acid suppression and national recommendations emphasize limiting use of antireflux medicines in infants.[14,37-43] In the present study, we found no benefit of acid suppression on subsequent visits, reinforcing that they should not be prescribed for suspected reflux in BRUE.

A final misconception about BRUE is that these patients have no recurrent symptoms. However, we found that patients continue to present with similar and/or ongoing symptoms with costs totaling up to $7000 per patient in the 6 months following BRUE. More than one-quarter of patients were either readmitted or seen in the ED for similar symptoms during follow-up, contradicting the assumption that the initial BRUE hospitalization might serve a reassuring role. Others have suggested that patients with BRUE are not at increased risk for increased mortality.[44] In our cohort, however, there were 2 deaths, representing 0.6% of the presenting cohort.

Almost one-third of the subjects in our study were premature and notably, these subjects were even more likely to have abnormal swallow study results at the time of the BRUE presentation or after, a longer length of stay, and increased risk of repeat hospitalization. Premature subjects were also more likely to be treated with acid suppression. The AAP guidelines do report higher rates of BRUE in premature infants that are born at less than 32 weeks of gestational age and suggest that such patients fall into the higher risk BRUE category.[4] Our results support this additional consideration for premature infants presenting after BRUE and highlight that this group is at particular risk for oropharyngeal dysphagia and may benefit from early performance of VFSS.

Recognizing the high rate of re-presentation for persistent symptoms and recognizing the high costs associated with care of these patients, we believe that the current guideline would be strengthened by recommending objective assessment of swallowing and feeding interventions along with removal of GERD from consideration as an explanatory model for BRUE, changes which are low risk interventions with potential to reduce hospitalization and cost. Our recommended approach for these patients would include testing with VFSS and/or empiric thickening of feeds in collaboration with feeding experts while awaiting VFSS, particularly at centers where coordination of VFSS can be more of a challenge and might significantly delay discharge. We also recommend based on this study and others in the past that acid suppression should be avoided as its use does not improve outcomes.[14] Future studies will be needed to show that treatment of swallowing dysfunction improves outcomes and decreases the incidence of BRUE.

There are several potential limitations to the present study. It is possible that there were unmeasured differences in the patient populations in the years before and after AAP guideline publication. However, for both years we used *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* codes and also reviewed charts to make sure all subjects fit the AAP definition. We found no differences in any characteristics to suggest the populations differed. In addition, although Boston Children's Hospital is a tertiary referral center and the possibility exists that our patients with BRUE may not represent the same population as those seen in other hospitals, more than 78% of patients came from the Boston metropolitan area, suggesting this population is not a referral population. It is also important to recognize that there might be a delay between the time of guideline publication and the widespread implementation of the guideline into practice. At our institution, the AAP guidelines were reviewed and a new clinical practice approach agreed upon in the spring of 2016, but it is possible that not all providers immediately incorporated the recommendations into their clinical approach to patients with BRUE. Lastly, it is possible that decisions about obtaining VFSS or other testing may have

been affected by breastfeeding status or other unmeasured factors including family preferences; this must be assessed by a prospective multicenter study with inclusion of all infants to reduce bias. ■

Submitted for publication Dec 14, 2018; last revision received Apr 2, 2019; accepted Apr 4, 2019.

Reprint requests: Rachel L. Rosen, MD, MPH, Aerodigestive Center, Division of Gastroenterology, Hepatology, and Nutrition, Boston Children's Hospital, 300 Longwood Ave, Boston, MA 02115. E-mail: Rachel.Rosen@childrens.harvard.edu

References

1. Tieder JS, Altman RL, Bonkowsky JL, Brand DA, Claudius I, Cunningham DJ, et al. Management of apparent life-threatening events in infants: a systematic review. J Pediatr 2013;163:94-9.e1-6.
2. McGovern MC, Smith MB. Causes of apparent life threatening events in infants: a systematic review. Arch Dis Childhood 2004;89:1043-8.
3. Piumelli R, Davanzo R, Nassi N, Salvatore S, Arzilli C, Peruzzi M, et al. Apparent Life-Threatening Events (ALTE): Italian guidelines. Italian J Pediatr 2017;43:111.
4. Tieder JS, Bonkowsky JL, Etzel RA, Franklin WH, Gremse DA, Herman B, et al. Brief resolved inexplained events (formerly apparent life-threatening events) and evaluation of lower-risk infants. Pediatrics 2016;137.
5. Arane K, Claudius I, Goldman RD. Brief resolved unexplained event: new diagnosis in infants. Can Fam Phys Medecin de famille Canadien 2017;63:39-41.
6. National Institutes of Health Consensus Development Conference on Infantile Apnea and Home Monitoring, Sept 29 to Oct 1, 1986. Pediatrics 1987;79:292-9.
7. Jarasvaraparn C, Gallegos MBR, Mulekar MS, Bin W, Gremse DA, Crissinger KD. Short article: the endoscopic and histologic findings of infants who have experienced brief resolved unexplained events. Eur J Gastroenterol Hepatol 2018;30:195-200.
8. Duncan DR, Mitchell PD, Larson K, Rosen RL. Presenting signs and symptoms do not predict aspiration risk in children. J Pediatr 2018;201:141-6.
9. Weir KA, McMahon S, Taylor S, Chang AB. Oropharyngeal aspiration and silent aspiration in children. Chest 2011;140:589-97.
10. Duncan DR, Amirault J, Mitchell PD, Larson K, Rosen RL. Oropharyngeal dysphagia is strongly correlated with apparent life-threatening events. J Pediatr Gastroenterol Nutr 2017;65:168-72.
11. Hasenstab KA, Jadcherla SR. Respiratory events in infants presenting with apparent life threatening events: is there an explanation from esophageal motility? J Pediatr 2014;165:250-5.e1.
12. Vaquero-Sosa E, Francisco-Gonzalez L, Bodas-Pinedo A, Urbasos-Garzon C, Ruiz-de-Leon-San-Juan A. Oropharyngeal dysphagia, an underestimated disorder in pediatrics. Revista espanola de enfermedades digestivas: organo oficial de la Sociedad Espanola de Patologia Digestiva 2015;107:113-5.
13. Rubin BK. The cruelest lies are often told in silence. Chest 2011;140:567.
14. Duncan DR, Mitchell PD, Larson K, McSweeney ME, Rosen RL. Association of proton pump inhibitors with hospitalization risk in children with oropharyngeal dysphagia. JAMA Otolaryngology–Head Neck Surg 2018 Oct 11, in press.
15. Murphy SN, Weber G, Mendis M, Gainer V, Chueh HC, Churchill S, et al. Serving the enterprise and beyond with informatics for integrating biology and the bedside (i2b2). JAMIA 2010;17:124-30.
16. Gurberg J, Birnbaum R, Daniel SJ. Laryngeal penetration on videofluoroscopic swallowing study is associated with increased pneumonia in children. Int J Pediatr Otorhinolaryngol 2015;79:1827-30.
17. Serel Arslan S, Demir N, Karaduman AA. Both pharyngeal and esophageal phases of swallowing are associated with recurrent pneumonia in pediatric patients. Clin Respir J 2016;12:767-71.
18. Duncan DR, Larson K, Davidson K, May K, Rahbar R, Rosen RL. Feeding interventions are associated with improved outcomes in children with laryngeal penetration. J Pediatr Gastroenterol Nutr 2018;68:218-24.
19. Arvedson JC, Lefton-Greif MA. Instrumental assessment of pediatric dysphagia. Semin Speech Language 2017;38:135-46.
20. Hiorns MP, Ryan MM. Current practice in paediatric videofluoroscopy. Pediatr Radiol 2006;36:911-9.
21. Jadcherla SR, Stoner E, Gupta A, Bates DG, Fernandez S, Di Lorenzo C, et al. Evaluation and management of neonatal dysphagia: impact of pharyngoesophageal motility studies and multidisciplinary feeding strategy. J Pediatr Gastroenterol Nutr 2009;48:186-92.
22. Rangarathnam B, McCullough GH. Utility of a clinical swallowing exam for understanding swallowing physiology. Dysphagia 2016;31:491-7.
23. DeBoer EM, Kinder S, Duggar A, Prager JD, Soden J, Deterding RR, et al. Evaluating the yield of gastrointestinal testing in pediatric patients in aerodigestive clinic. Pediatr Pulmonol 2018;53:1517-24.
24. Greifer M, Santiago MT, Tsirilakis K, Cheng JC, Smith LP. Pediatric patients with chronic cough and recurrent croup: the case for a multidisciplinary approach. Int J Pediatr Otorhinolaryngol 2015;79:749-52.
25. Boesch RP, Balakrishnan K, Acra S, Benscoter DT, Cofer SA, Collaco JM, et al. Structure and functions of pediatric aerodigestive programs: a consensus statement. Pediatrics 2018;141.
26. Boesch RP, Balakrishnan K, Grothe RM, Driscoll SW, Knoebel EE, Visscher SL, et al. Interdisciplinary aerodigestive care model improves risk, cost, and efficiency. Int J Pediatr Otorhinolaryngol 2018;113:119-23.
27. Horton J, Atwood C, Gnagi S, Teufel R, Clemmens C. Temporal trends of pediatric dysphagia in hospitalized patients. Dysphagia 2018;33:655-61.
28. Bhattacharyya N. The prevalence of pediatric voice and swallowing problems in the United States. Laryngoscope 2015;125:746-50.
29. Hersh C, Wentland C, Sally S, de Stadler M, Hardy S, Fracchia MS, et al. Radiation exposure from videofluoroscopic swallow studies in children with a type 1 laryngeal cleft and pharyngeal dysphagia: a retrospective review. Int J Pediatr Otorhinolaryngol 2016;89:92-6.
30. McFarlin A. What to do when babies turn blue: beyond the basic brief resolved unexplained event. Emerg Med Clin N Am 2018;36:335-47.
31. Mittal MK, Donda K, Baren JM. Role of pneumography and esophageal pH monitoring in the evaluation of infants with apparent life-threatening event: a prospective observational study. Clin Pediatr (Phila) 2013;52:338-43.
32. Smits MJ, van Wijk MP, Langendam MW, Benninga MA, Tabbers MM. Association between gastroesophageal reflux and pathologic apneas in infants: a systematic review. Neurogastroenterol Motility 2014;26:1527-38.
33. Puntis JW, Booth IW. ALTE and gastro-oesophageal reflux. Arch Dis Childhood 2005;90:653. author reply.
34. Zimbric G, Bonkowsky JL, Jackson WD, Maloney CG, Srivastava R. Adverse outcomes associated with gastroesophageal reflux disease are rare following an apparent life-threatening event. J Hosp Med 2012;7:476-81.
35. Mousa H, Woodley FW, Metheney M, Hayes J. Testing the association between gastroesophageal reflux and apnea in infants. J Pediatr Gastroenterol Nutr 2005;41:169-77.
36. Scherer LD, Zikmund-Fisher BJ, Fagerlin A, Tarini BA. Influence of "GERD" label on parents' decision to medicate infants. Pediatrics 2013;131:839-45.
37. Stark CM, Nylund CM. Side Effects and complications of proton pump inhibitors: a pediatric perspective. J Pediatr 2016;168:16-22.
38. Rosen R, Hu L, Amirault J, Khatwa U, Ward DV, Onderdonk A. 16S community profiling identifies proton pump inhibitor related differences in gastric, lung, and oropharyngeal microflora. J Pediatr 2015;166:917-23.
39. Freedberg DE, Lamouse-Smith ES, Lightdale JR, Jin Z, Yang YX, Abrams JA. Use of acid suppression medication is associated with risk for *C. difficile* infection in infants and children: a population-based study. Clin Infect Dis 2015;61:912-7.

40. Brown KE, Knoderer CA, Nichols KR, Crumby AS. Acid-suppressing agents and risk for *Clostridium difficile* infection in pediatric patients. Clin Pediatr (Phila) 2015;54:1102-6.
41. Rosen R, Amirault J, Liu H, Mitchell P, Hu L, Khatwa U, et al. Changes in gastric and lung microflora with Acid suppression: acid suppression and bacterial growth. JAMA Pediatr 2014;168:932-7.
42. Rosen R, Vandenplas Y, Singendonk M, Cabana M, DiLorenzo C, Gottrand F, et al. Pediatric gastroesophageal reflux clinical practice guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutri 2018;66:516-54.
43. Duncan DR, Amirault J, Johnston N, Mitchell P, Larson K, Rosen RL. Gastroesophageal reflux burden, even in children that aspirate, does not increase pediatric hospitalization. J Pediatr Gastroenterol Nutr 2016;63:210-7.
44. Brand DA, Fazzari MJ. Risk of death in infants who have experienced a brief resolved inexplained event: a meta-analysis. J Pediatr 2018;197:63-7.

50 Years Ago in *The Journal of Pediatrics*

Initial Urinary Tract Infections, Observations in Children without Major Radiologic Abnormalities

Forbes PA, Drummond KN, Nogrady MB. J Pediatr 1969;75:187-92.

Urinary tract infections have been a cause of concern for more than 50 years in view of their association with renal injury. The development of imaging studies has improved the management of affected subjects.

Forbes et al published clinical, bacteriologic, and radiologic data for 90 children after their first urinary tract infection. Children were between 3 months and 16 years of age. Follow-up varied from 9 to 42 months. All patients had an intravenous pyelogram and a voiding urethrocystography (VCUG) at the end of treatment, and patients with gross radiologic abnormalities were excluded. Still, more than one-half of patients had minor abnormalities; the 2 most frequently encountered were urethral or meatal stenosis and reflux. The authors highlight the importance of follow-up, especially in these patients, noting their high rate of recurrence.

Throughout the last 50 years, the diagnosis and management of urinary tract infections have been topics of controversy and constant evolution. Recommended clinical guidelines from pediatric, urology, or nephrology associations have varied to some degree. The timing and selection of imaging studies for these patients have also evolved. Intravenous pyelogram has been completely supplanted by the noninvasive, nonradiating ultrasound. Also, up until a few years ago all small children were required to have a VCUG after their first febrile infection. Recently, there is a tendency to restrict such studies because of radiation exposure, risk of iatrogenic infection during urethral catheterization, stress, cost, and questionable efficacy of antibiotic prophylaxis in low risk patients. VCUG is now reserved for children with a febrile urinary infection only if the ultrasound detects abnormalities. Better technology has also permitted us to detect clinically important urologic malformations before birth with prenatal ultrasounds in the third trimester. Nuclear imaging studies also allow us to observe renal scarring.

The study by Forbes et al was one of the first to underline the importance of follow-up in children with urinary tract infections. Decades have passed, and we are still discussing how to best manage our patients.

Iyali M. Corrales-Cambero, MD
Pediatric Nephrology Department

Giordano Pérez-Gaxiola, MD
Evidence-Based Medicine Department
Hospital Pediátrico de Sinaloa
Culiacán, Mexico

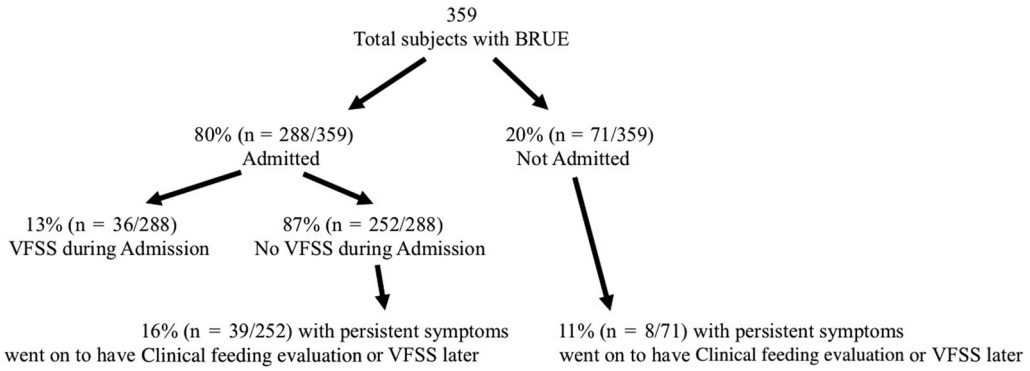

Figure 1. Flow diagram of study population showing proportion of subjects with BRUE admitted and seen in ED, along with clinical feeding evaluation and VFSS testing rates during and after initial BRUE evaluation.

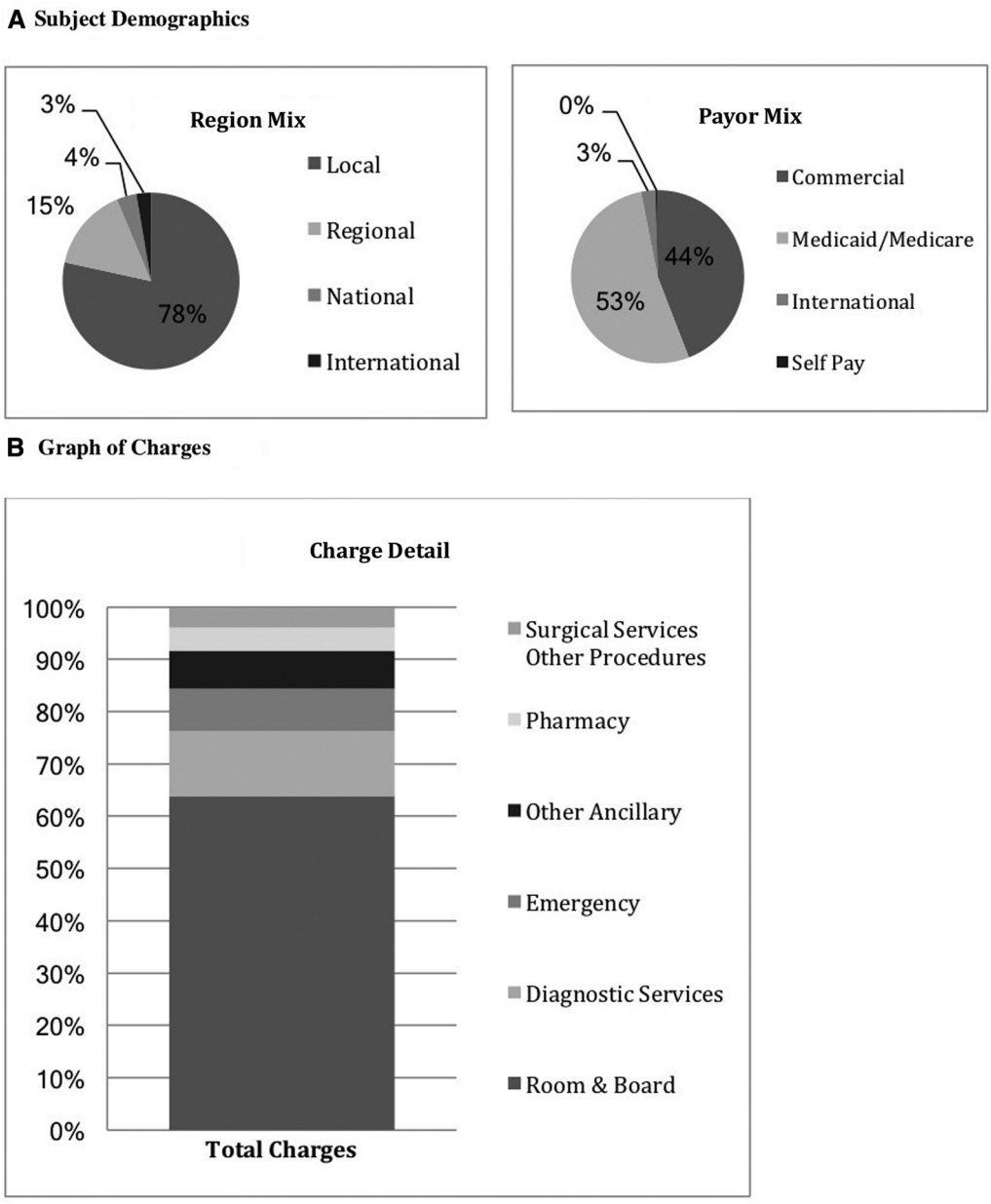

Figure 2. **A,** Subject demographics. **B,** Graph of charges. **A,** shows that the patient population was primarily local with a mix of commercial and state insurance. **B,** shows the distribution of charges for all BRUE presentations, consisting largely of charges for room and board, diagnostic testing and ED care.

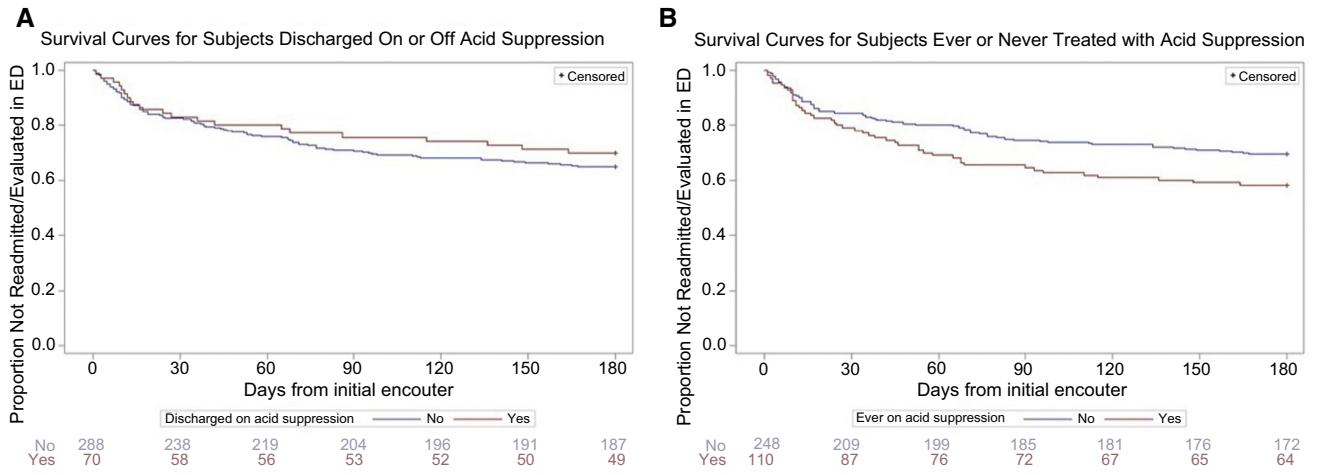

Figure 4. Kaplan-Meier curves for treatment with acid suppression and risk of repeat admission or ED visit. Kaplan-Meier curves showing risk of subsequent admission or ED visit for **A,** subjects discharged on acid suppression (P = .28) in and **B,** subjects ever treated with acid suppression (P = .08) in, showing no benefit of acid suppression in BRUE.

Table III. Clinical feeding evaluation results

Clinical feeding evaluation	Pre-algorithm (n = 186)	Post-algorithm (n = 173)	*P* value
Clinical feeding evaluation performed Ever	68/186 (37)*	57/173 (33)	.51
During admission	48/186 (26)	41/173 (24)	.71
After admission	19/186 (10)	16/173 (9)	.86
Clinical feeding evaluation results Normal	31/68 (46)	27/57 (47)	.58
Concern for aspiration/penetration	16/68 (24)	12/57 (21)	.53
Discoordination	14/68 (21)	18/57 (32)	.51
Change in management	33/68 (49)	30/57 (53)	.36
Change in flow rate	8/33 (24)	25/30 (83)	<.001
Thickening	3/33 (9)	0/30 (0)	.10
Recommend VFSS	15/33 (46)	5/30 (17)	.003

Proportion with clinical feeding evaluation, findings on clinical feeding evaluation, and change in management based on clinical feeding evaluation results, showing a significant increase in proportion for which change in bottle flow rate was recommended, decrease in recommendation for thickening, and fewer subjects sent for confirmatory VFSS.
*n (%).

Table V. Liquid consistencies recommended after VFSS

Consistency recommended after swallow study	Pre-algorithm (n = 44 with VFSS)	Post-algorithm (n = 35 with VFSS)	*P* value
Thin liquid consistency	24 (54)*	23 (65)	.36
Half-nectar consistency	6 (14)	8 (23)	.38
Nectar consistency	7 (16)	1 (3)	.07
Half-honey consistency	0 (0)	1 (3)	.44
Honey consistency	1 (2)	2 (6)	.58
NPO after VFSS	6 (14)	0 (0)	.03

Liquid consistencies recommended after VFSS in the year before and the year after BRUE guidelines.
*n (%).

Table VII. Association between acid suppression and repeat admission or ED visit

Exposures	n*/n†	Univariate HR (95% CI)	Univariate *P* value	Multivariate‡ HR (95% CI)	Multivariate‡ *P* value
Discharged on acid suppression					
No	102/289	1.00		1.00	
Yes	21/70	0.83 (0.52,1.32)	.43	0.76 (0.47,1.25)	.28
Ever on acid suppression					
No	76/248	1.00		1.00	
Yes	47/111	1.48 (1.03,2.13)	.04	1.42 (0.96,2.11)	.08

Results of Cox proportional hazards analysis comparing time to repeat ED visit and/or hospitalization for subjects that were or were not discharged on or ever treated with acid suppression, showing no significant difference in HR for any comparison group.
*Number with admission or ED visit.
†Total number at risk.
‡Multivariate adjustment for age at initial presentation, sex, premature status at birth, and total number of diagnostic tests performed during initial hospitalization.