



# Premiere Publications from The Triological Society

Read all three of our prestigious publications, each offering high-quality content to keep you informed with the latest developments in the field.

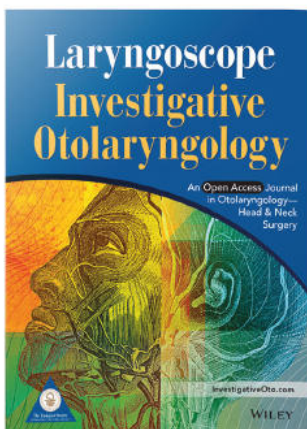


## THE Laryngoscope FOUNDED IN 1896

Editor-in-Chief: Michael G. Stewart, MD, MPH

The leading source for information in head and neck disorders.

[Laryngoscope.com](http://Laryngoscope.com)



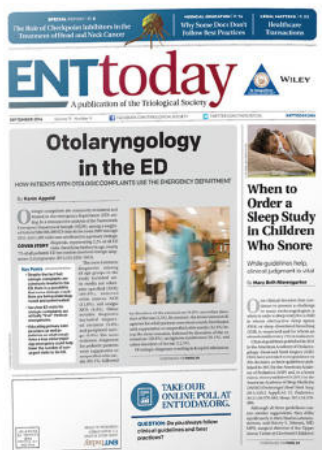
## Laryngoscope Investigative Otolaryngology

Open Access

Editor-in-Chief: D. Bradley Welling, MD, PhD, FACS

Rapid dissemination of the science and practice of otolaryngology-head and neck surgery.

[InvestigativeOto.com](http://InvestigativeOto.com)



## ENTtoday

A publication of the Triological Society


Editor-in-Chief: Alexander Chiu, MD

Must-have timely information that Otolaryngologist-head and neck surgeons can use in daily practice.

[Enttoday.org](http://Enttoday.org)

WILEY

# pH-Neutralizing Esophageal Irrigations as a Novel Mitigation Strategy for Button Battery Injury

Rachel R. Anfang, MA; Kris R. Jatana, MD ; Rebecca L. Linn, MD; Keith Rhoades, BS; Jared Fry, BS; Ian N. Jacobs, MD

**Objectives/Hypothesis:** Ingestion of button batteries (BB) can rapidly lead to caustic esophageal injury in infants and children, resulting in significant morbidity and mortality. To identify novel mitigation strategies, we tested common weakly acidic household beverages, viscous liquids, and Carafate<sup>®</sup> for their ability to act as protective esophageal irrigations until endoscopic removal of the BB.

**Study Design:** Cadaveric and live animal model.

**Methods:** Apple juice, orange juice, Gatorade<sup>®</sup>, POWERADE<sup>®</sup>, pure honey, pure maple syrup, and Carafate<sup>®</sup> were screened using a 3V lithium (3V-CR2032) BB on cadaveric porcine esophagus. The most promising in vitro options were tested against a saline control in live American Yorkshire piglets with anode-facing placement of the BB on the posterior wall of the proximal esophagus for 60 minutes. BB voltage and tissue pH were measured before battery placement and after removal. The 10 mL irrigations occurred every 10 minutes from t = 5 minutes. Gross and histologic assessment was performed on the esophagus of piglets euthanized 7 ± 0.5 days following BB exposure.

**Results:** Honey and Carafate<sup>®</sup> demonstrated a significant degree the most protective effects in vitro and in vivo. Both neutralized the tissue pH increase and created more localized and superficial injuries; observed in vivo was a decrease in both full-thickness injury (i.e., shallower depths of necrotic and granulation tissue) and outward extension of injury in the deep muscle beyond surface ulcer margins ( $P < .05$ ).

**Conclusions:** In the crucial period between BB ingestion and endoscopic removal, early and frequent ingestion of honey in the household setting and Carafate<sup>®</sup> in the clinical setting has the potential to reduce injury severity and improve patient outcomes.

**Key Words:** Foreign body, button battery, esophageal injury, caustic injury, prevention, neutralization.

**Level of Evidence:** NA

*Laryngoscope*, 00:000-000, 2018

From the Division of Otolaryngology, Department of Surgery (R.R.A., I.N.J.); Division of Anatomic Pathology, Department of Pathology and Laboratory Medicine (R.L.L.), Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; Department of Otolaryngology-Head and Neck Surgery (K.R.J.), Nationwide Children's Hospital and Wexner Medical Center at Ohio State University, Columbus, Ohio; Intertek Product Intelligence Group Inc (K.R., J.F.), Oakbrook, Illinois; and the Department of Otorhinolaryngology-Head and Neck Surgery (I.N.J.), Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, U.S.A.

Editor's Note: This Manuscript was accepted for publication May 3, 2018.

K.R.J. and I.N.J. are co-principal investigators.

Presented orally, as the winner of the Broyles Maloney Award, at the American Broncho-Esophagological Association Meeting, National Harbor, Maryland, U.S.A., April 18-22, 2018.

K.R.J. serves as a general product safety medical consultant for Intertek Inc., provides expert witness testimony, and receives royalties for a patented medical device, unrelated and not utilized in this study from Marpac Inc. Both K.R.J. and I.N.J. serve in leadership positions on the national Button Battery Task Force, affiliated with the American Academy of Pediatrics and American Broncho-Esophagological Association.

This work was supported by the Children's Hospital of Philadelphia through its Frontiers Program Grant (I.N.J.).

The authors have no other funding, financial relationships, or conflicts of interest to disclose.

Send correspondence to Kris R. Jatana, MD, Pediatric Otolaryngology, Nationwide Children's Hospital, 555 South 18th Street, Suite 2A, Columbus, OH 43205. E-mail: kris.jatana@nationwidechildrens.org

DOI: 10.1002/lary.27312

## INTRODUCTION

Over 3,000 button battery (BB) ingestions are reported annually in the United States.<sup>1,2</sup> Although this comprises a small fraction of pediatric foreign bodies ingestions, BB contribute a serious risk of morbidity and mortality with the problem only worsening. There was a 5.8-fold increase in major injuries and a 12.5-fold increase in fatal outcomes in 2006 to 2017 versus 1994 to 2005.<sup>2</sup>

The growth of electronics in prevalence and complexity resulted in BBs becoming ubiquitous in our everyday environments, with many being the powerful 3V lithium variety.<sup>2,3</sup> Strikingly, greater than 90% of disk-battery ingestion cases resulting in fatalities or major outcomes over the last 15 years were from 20 mm, 3V lithium cells, of which more than 70% were 3V-CR2032 BBs.<sup>1</sup> At this diameter and voltage, they are large enough to get lodged in the esophagus of a child and powerful enough to cause major sequelae or death. The inherent characteristics of a BB—the shiny, candy-resembling shape, metallic taste, and tingling sensation on the tongue—intensify this concern by appealing to the natural curiosity of a toddler. In fact, at highest risk for reported ingestions are children under 6 years of age, and 12.6% of this cohort experienced major complications.<sup>2,3</sup>

Serious damage can occur in as little as 2 hours after esophageal impaction due to the mechanism and speed of injury development.<sup>1,3,4</sup> As our previous research demonstrated, the circuit closes and causes water in the mucosa to hydrolyze within minutes of the BB making contact with electrolyte-rich esophageal tissue.<sup>4</sup> Although the hydrogen gas is harmlessly released, the remaining hydroxide-rich, alkaline solution creates a caustic injury with liquefactive necrotic features.

With longer injury times, postremoval clinical course can be complicated by delayed esophageal perforation or nonfunctional scar tissue formation, as the remaining viable tissue delineates.<sup>4</sup> Thus, injury development and, consequently, the clinical outcomes are exacerbated by the manner in which children may initially present—asymptomatic or with nonspecific symptoms.<sup>4,5</sup> Even in cases of witnessed ingestion, emergent BB removal may be delayed by transport to specialized centers, as not all hospitals are staffed with pediatric anesthesiologists and endoscopists trained in foreign body removal. This is particularly true in rural and suburban areas.

Efforts to ameliorate the BB problem have focused predominantly on primary prevention.<sup>1,3,5</sup> Little has gone into developing treatments for the “golden window” (i.e., the interval after BB ingestion and before its endoscopic removal), to halt or reduce injury progression.<sup>6</sup> Our previous work on weak acid neutralization at the time of BB removal as a mitigation strategy resulted in updating the National Capital Poison Center management guidelines.<sup>4,7</sup> At time of removal, 0.25% acidic acid neutralization at the site of esophageal injury is now recommended, in the absence of a visible perforation.<sup>7</sup>

Advancing our foundational work, this study investigated weakly acidic viscous solutions as a novel mitigation strategy for early protective pH neutralizing esophageal irrigations. Our two-pronged approach to slow the rate of esophageal injury for witnessed or suspected button battery ingestion was as follows: 1) Could we identify a solution that is commonly found in the average home setting for immediate intervention? 2) Could Carafate<sup>®</sup>, a prescription antiulcer protectant, act as a beneficial medicinal option in a clinical setting prior to endoscopic removal?

## MATERIALS AND METHODS

### *In Vitro Injury Mitigation Experiments*

Frozen juvenile porcine cadaveric esophagi were defrosted to 22°C and sectioned into 6-cm segments. Each segment was opened along its length and positioned on a 15° incline. The pH of the tissue was measured using litmus paper (Jumbo; Micro Essential Laboratory, Brooklyn, NY). The voltage of the 3V-CR2032 BB (Duracell, Bethel, CT) was measured using a voltmeter (289 True RMS Multimeter; Fluke Corp., Everett, WA). Measurements were taken prior to BB placement and after its removal. The anode side of the battery was placed on the mucosal surface (t = 0 minutes), and the esophageal segment was washed with 10 mL of saline. The excess tissue was folded over the cathode to mimic an intact esophagus. Serial irrigations with 10 mL of a solution of interest (Table I) occurred every 10 to 15 minutes starting at t = 10 minutes. Prior to initial use,

the native pH of each solution was measured. Additional tissue pH measurements were recorded before irrigations by uncovering and lifting the BB to expose the tissue, then returning it to its original place. At t = 120 minutes, the battery was removed and photographs were taken of the injury. These experiments were performed in duplicate at Intertek, Inc. (Arlington Heights, IL) and were exempt from oversight by the Institutional Animal Care and Use Committees (IACUC) at Children's Hospital of Philadelphia (CHOP) and Nationwide Children's Hospital.

### *In Vivo Injury Mitigation Experiments*

American Yorkshire piglets weighing 10 to 11 kg were anesthetized to a surgical plane of depth using isoflurane (0.5%–5%) and propofol (4–8 mg/kg intravenous [IV] induction, 12 mg/kg/hr IV maintenance), with endotracheal intubation. The piglet was placed in a supine position with its head supported at approximately a 30° angle. Access to the proximal esophagus was secured with a Miller blade laryngoscope. The anode face of the BB was situated against the posterior wall of the proximal esophagus, adjacent to hypopharynx, and 10 mL of saline were administered (t = 0 minutes). The BB remained in place for the entire 60-minute duration for irrigations in the *in vivo* study. This 60-minute experimental timeframe was selected to be in compliance with IACUC protocol; the pilot study animal could not survive for a full week when a longer BB exposure duration was attempted. Prior to BB insertion and after its removal, the pH of the proximal esophagus and the voltage of the BB were measured. Serial irrigations with either saline, Carafate<sup>®</sup> suspension (1 g/10 mL), or Gunther's Pure Clover Honey occurred every 10 minutes starting at t = 5 minutes. Solutions were delivered through a syringe locked to a rigid suction tube (3 mm × 35 cm; Karl Storz Endoscopy America, El Segundo, CA) or a cut 4.5-mm endotracheal tube. Visualization was done endoscopically (0° Hopkins telescope, 2.9 mm × 30 cm and All-In-One Telepack X LED Video System; Karl Storz). The piglets were given Buprenorphine SR (0.1 mg/kg subcutaneous once) for analgesia, awakened, extubated, and left to recover for 7 ± 0.5 days on a regular chow diet supplemented with wet dog food, fruits, and vegetables. The study strictly adhered to a CHOP IACUC approved protocol.

### *Organ Removal for Histological Evaluation*

On day 7 ± 0.5, the piglets were euthanized using phenobarbital/phenytoin sodium (Euthasol, Beuthanasia-D; 125 mg/kg IV) and a confirmatory thoracotomy. The proximal esophagus was surgically removed. After the injury was identified and photographed, the tissue was stored in 10% formalin.

### *Gross Analysis of the Injured Esophageal Tissue*

After at least 24 hours in formalin, the tissue was trimmed to the area of interest and imaged with a ruler for scale. The length and width of the visible surface injury was measured, and its surface area was calculated.

### *Histologic Analysis of the Injured Esophageal Tissue*

The trimmed specimens were serially sectioned to a thickness of 5 mm and submitted for histologic analysis along with sections of distal tissue, which served as internal healthy tissue controls. Slides from the paraffin-embedded tissue blocks were stained with hematoxylin and eosin (HE). Depths of necrosis and granulation tissue (percentage of tissue thickness) as well

TABLE I.  
Solutions Tested In Vitro, Juvenile Cadaveric Porcine Esophageal Model.

Product	pH of Product	Final pH of Tissue	Neutralization Effectiveness
Honey: Madhava Very Raw (Brazil)	4.0	4.5	Ideal
Honey: Makuna Bio Active (New Zealand)	4.0	4.8	Ideal
Honey: Raw Organic Honey (Brazil)	5.0	5.0	Ideal
Honey: Buzz & Bloom Bold (Vietnam)	4.0	5.5	Ideal
Honey: Crockett Arizona Wildflower (Arizona, USA)	5.0	5.5	Ideal
Honey: Gunter's Honey Clover (Virginia, USA)	4.0	6.0	Ideal
Honey: Linden Smiley Unfiltered (Italy)	6.0	6.0	Ideal
Honey: Nature Nate's Raw & Unfiltered (Texas, USA)	5.0	7.5	Ideal
Carafate <sup>®</sup>	4.0	7.5	Ideal
Motts <sup>®</sup> apple juice	3.7	9.0	Partial
Store brand orange juice	4.2	9.5	Partial
POWERADE <sup>®</sup> mountain blast	2.8	10.5	Minimal, no benefit
Gatorade <sup>®</sup> fruit punch	3.1	11.0	Minimal, no benefit
POWERADE <sup>®</sup> fruit punch	2.7	11.5	Minimal, no benefit
POWERADE <sup>®</sup> lemon-lime	2.7	11.5	Minimal, no benefit
Gatorade <sup>®</sup> lemon-lime	3.0	11.5	Minimal, no benefit
Store brand maple syrup	4.7	11.5	Minimal, no benefit
Gatorade <sup>®</sup> berry blue	3.0	12.0	Minimal, no benefit
Simulated saliva	6.3	12.8	No benefit
0.9% sodium chloride control	5.6	13.0	No benefit

Solutions were screened in vitro for their ability to neutralize the alkaline increase in tissue pH related to contact between the button battery and esophageal mucosa (initial pH = 7.0 ± 0.2). 3V-CR2032 button battery was placed with anode face on the mucosal tissue of juvenile cadaveric porcine esophageal segments. Over a 120-minute period starting at t = 5 minutes, 10 mL of solution were administered at 10- to 15-minute intervals. Solutions were tested in duplicate and listed by their relative effectiveness with only two types performing ideally: honey (all varieties) most optimally and Carafate<sup>®</sup> still within the optimal range.

as muscular structure (number and distance of necrotic breaks in the muscularis propria and injury extension beyond the surface ulcer perimeter) were measured using an ocular micrometer. The quality of the injured and healed tissue was evaluated using Masson's trichrome on select sections. Imaging was performed using a Nikon microscope camera DS-Fi3 (Nikon Corp., Tokyo, Japan).

### Statistics

For each outcome, multiple comparison analysis was performed by one- or two-way analysis of variance with post hoc Tukey correction using the calculated mean, standard deviation, and the number of subjects for each treatment group (or subgroups). For the in vitro experiments, n = 2 for Carafate<sup>®</sup> and the controls, and n = 16 for honey, representing an aggregate of the eight brands tested. For the in vivo experiments, n = 2 for honey, n = 3 for Carafate<sup>®</sup>, and n = 4 for saline (with n = 2 for the perforating control [PC] and nonperforating control [NPC] subgroups). P values < .05 were considered significant. Five animals were excluded from analysis due to inconsistent methodology or anesthetic complications.

### RESULTS

The solutions tested in vitro on juvenile porcine cadaveric esophageal segments were categorized by their relative mitigation effectiveness (Table I). Saline performed similarly to the simulated saliva (P < .05). For this reason, as well as because of its preferable homogeneity and stability characteristics and its use to simulate swallowing saliva in repeated trials of anesthetized

animals, saline was utilized as the control across the in vitro and in vivo studies. Only honey and Carafate<sup>®</sup> neutralized the increased tissue pH at the battery application site to clinically optimal levels (Table I) and statistically significant degrees compared to the saline control (Fig. 1). This held true with their ability to reduce injury severity on cadaveric tissue (Fig. 2). Conversely, saline-treated tissue maintained a highly alkaline pH and developed a greater visible injury.

Based on the in vitro results, honey and Carafate<sup>®</sup> were tested in vivo against saline. Each group performed similarly in vivo as they did in vitro. Honey was more effective than Carafate<sup>®</sup>, and both were significantly better than saline at slowing the discharge of the BB and neutralizing the tissue pH increase (Fig. 3A,B). Grossly, the area of the surface ulcer did not significantly differ between the groups (Fig. 3C). However, the severity of injury was markedly different (Fig. 4). Half of the control animals developed delayed esophageal perforations, whereas, no honey- or Carafate<sup>®</sup>-treated animals experienced this severe complication.

Assessment of the HE-stained sections revealed significantly greater depths of dead necrotic tissue, and healing granulation tissue were present at significantly deeper levels in the control than in the two treatment groups (Fig. 5A,B). Furthermore, the quality of the esophageal deep muscle layer of the esophagus (i.e., muscularis propria) varied significantly with the control group showing the most extensive destruction (Fig.

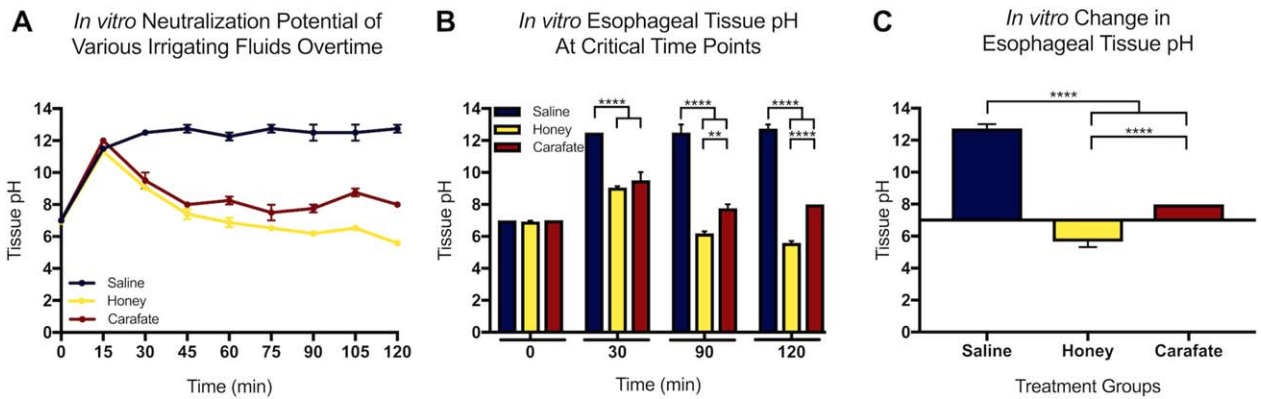


Fig. 1. The mucosal surface of cadaveric porcine esophageal tissue exposed to the anode side of a 3V-CR2032 button battery (BB) underwent serial 10-mL irrigations at 10- to 15-minute intervals with a solution of interest starting at  $t = 10$  minutes. (A) pH readings of the tissue at the BB application site were recorded over a 2-hour time period. (B) Honey and Carafate<sup>®</sup> are significantly better at neutralization within two irrigations compared to the control ( $t = 30$  minutes). Honey performed better than Carafate<sup>®</sup>, and both were significantly better than the control at  $t = 90$  minutes. The statistical differences between groups were enhanced by the conclusion of the experiment ( $t = 120$  minutes) and (C) when the data were examined in absolute terms (i.e., as a  $\Delta$ pH  $n = 2$  for the saline control and Carafate<sup>®</sup>, and  $n = 16$  for honey), representing an aggregate of the eight brands tested. Data are shown as mean  $\pm$  standard error of the mean. \* $P < .05$ . \*\* $P < .01$ . \*\*\* $P < .001$ . \*\*\*\* $P < .0001$ . [Color figure can be viewed in the online issue, which is available at [www.laryngoscope.com](http://www.laryngoscope.com).]

5C,F). The average width of a full-thickness necrotic break in the muscle did not change with honey and Carafate<sup>®</sup> use, but the number of breaks and, consequently, the overall distance of muscular compromise was significantly reduced. Interestingly, the tissue injured was not localized to the area directly beneath the ulcerated surface mucosa. All groups experienced destruction in the muscularis propria extending beyond the visible surface injury with a significantly higher degree found in the control group.

Masson's trichrome stain highlighted the dual manner in which the control animals were at a disadvantage compared to the animals receiving a mitigating treatment. The degree of coagulative necrosis and damage to the muscle was more extensive with saline, and the density of reparative collagen fibrosis in areas of severe injury was more robust with honey and Carafate<sup>®</sup> (Fig. 6).

Significantly different injury patterns were observed not only across treatment groups but also

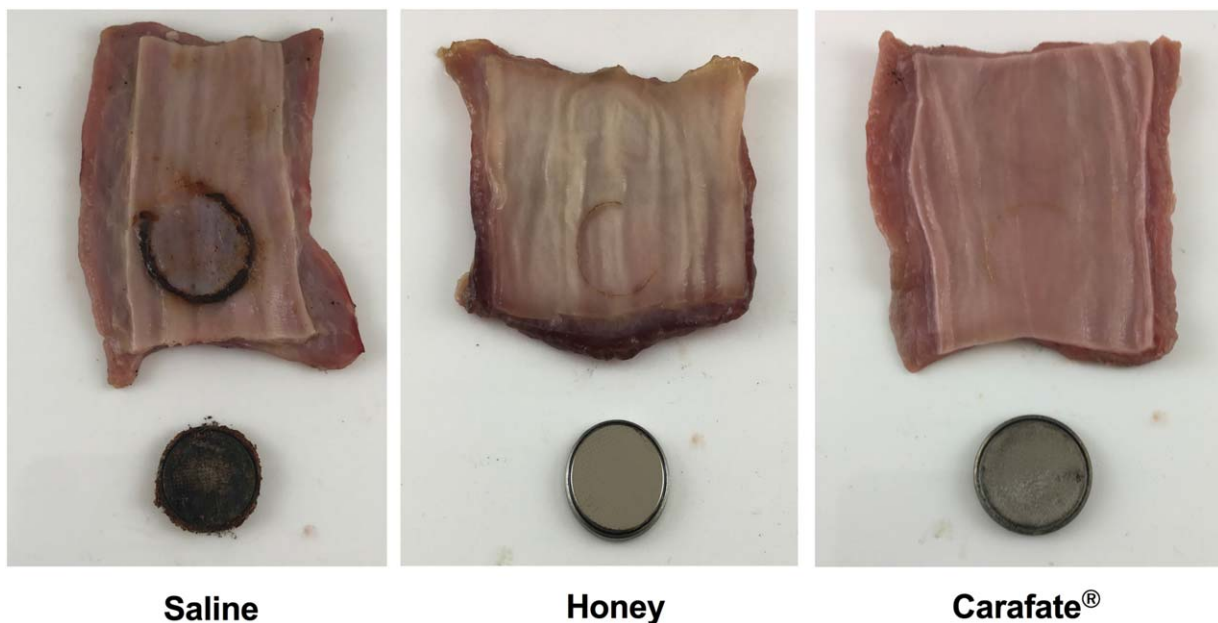


Fig. 2. The mucosal surface of cadaveric porcine esophageal tissue exposed to the anode side of a 3V-CR2032 button battery (BB) underwent serial 10-mL irrigations at 10- to 15-minute intervals with a solution of interest starting at  $t = 10$  minutes. Shown are representative images of the esophageal mucosa at the conclusion of the experiment ( $t = 120$  minutes) for each group. (A) Saline. (B) Carafate<sup>®</sup>. (C) Honey. Upon visual inspection of the surface injury, it was noted that both honey and Carafate<sup>®</sup> acted as protectants in vitro against the BB insult by reducing the severity of the injury compared to the saline control. [Color figure can be viewed in the online issue, which is available at [www.laryngoscope.com](http://www.laryngoscope.com).]

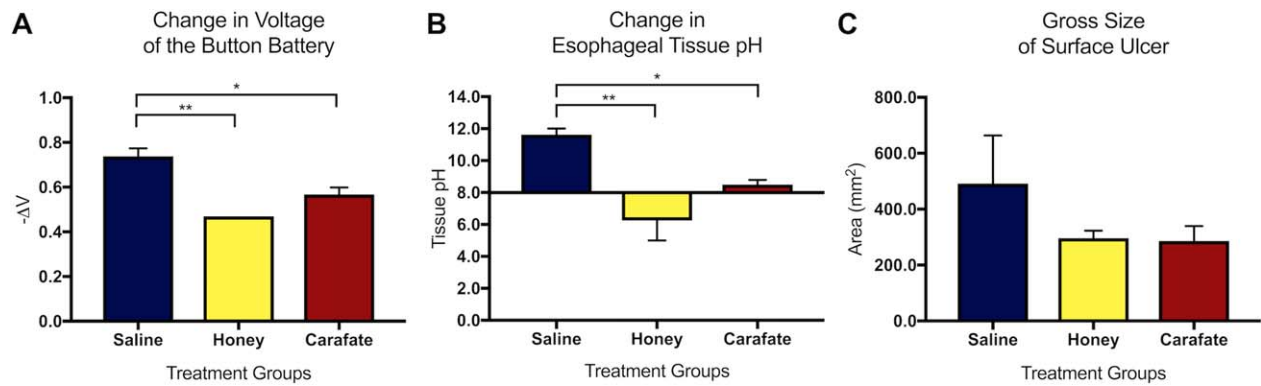


Fig. 3. Prior to inserting the button battery (BB) into the proximal esophagus of a live piglet and after its removal ( $t = 60$  minutes), (A) the BB voltage and (B) the pH of the tissue at the BB application site were measured, and their changes was calculated. The proximal esophagus was resected  $7 \pm 0.5$  days following BB exposure and fixed in 10% formalin for  $\geq 24$  hours. The mucosal surface of the fixed tissue was imaged using a ruler for scale. The area of surface ulceration was calculated from length and width measurements ( $n = 2, 3,$  and  $4$  for honey, Carafate<sup>®</sup>, and the saline control, respectively). Data are shown as mean  $\pm$  standard error of the mean. \* $P < .05$ . \*\* $P < .01$ . [Color figure can be viewed in the online issue, which is available at [www.laryngoscope.com](http://www.laryngoscope.com).]

between the control subgroups (Fig. 7A,B). The PC had larger surface ulcers with minimal extension of deep muscular injury beyond the ulcerative margins. The NPC had the opposite presentation. In contrast to both control subgroups, honey and Carafate<sup>®</sup> exhibited smaller ulcers like the NPC, but with minimal injury extension like the PC.

## DISCUSSION

The interval between BB ingestion and its endoscopic removal from the esophagus is a critical time period for intervention to curtail the rapid development of severe injury. Therefore, this study sought to characterize the esophageal injury by gross and microscopic changes after 1 to 2 hours of mucosal exposure to the anode face of a 3V lithium BB, and in this timeframe implement novel mitigation strategies that would

translate to all BB with the same mechanism of action (e.g., lithium, alkaline, and silver oxide).<sup>4</sup>

The in vivo study demonstrated an extensive pattern of necrosis in the saline control animals that extended to the adventitia, the deepest tissue layer, and damaged the muscularis propria in a larger radius than the visible surface ulcer would indicate. The 1-hour rate for severe injury development in vivo was faster than typically observed in pediatric patients. Possible explanations include: 1) experimental conditions—the animal's supine positioning and anesthesia-related paralysis as well as the precise placement of anode surface—allowing the battery to remain in constant contact with mucosal surface, and (2) gross and microscopic anatomical differences between pigs and humans.

Clinically, severe esophageal injury puts the patient at risk for vocal cord paralysis, functional motility

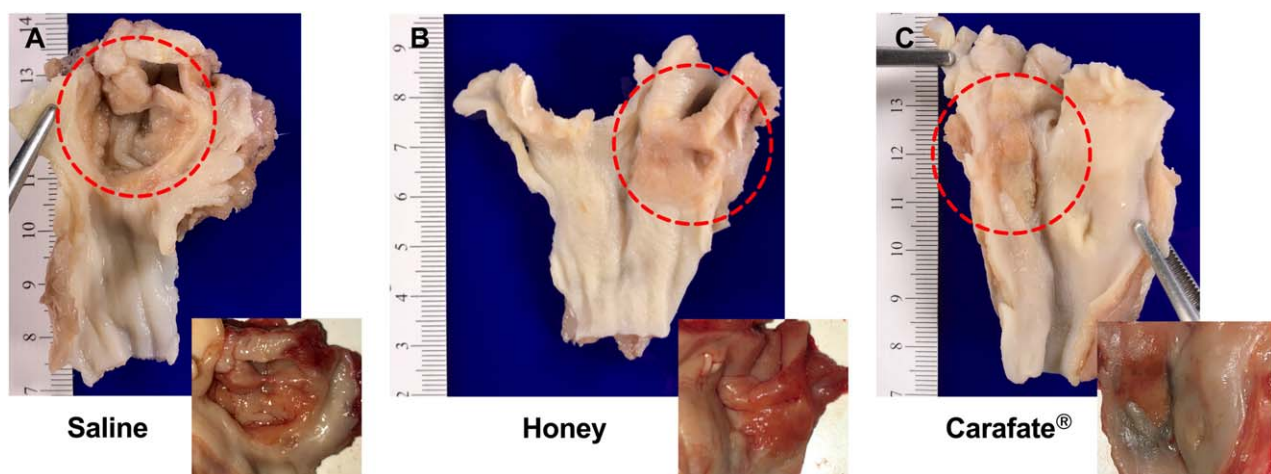


Fig. 4. The proximal esophagus was resected  $7 \pm 0.5$  days following button battery (BB) exposure and fixed in 10% formalin for  $\geq 24$  hours. Surface ulcerations (red arrows) on the fixed mucosa (main image) and at time of resection (inset image) are shown. (A) Saline-treated tissue with a deep perforation in the esophageal wall. The remaining intact wall belongs to the diverticular wall of a porcine esophagus, a structure that does not exist in a typical human esophagus. (B) Honey-treated tissue with a healing ulcerated surface. (C) Carafate<sup>®</sup>-treated tissue with a stained healing ulcerated surface. The discoloration was due to a reaction between the Carafate<sup>®</sup> and BB during treatment. [Color figure can be viewed in the online issue, which is available at [www.laryngoscope.com](http://www.laryngoscope.com).]

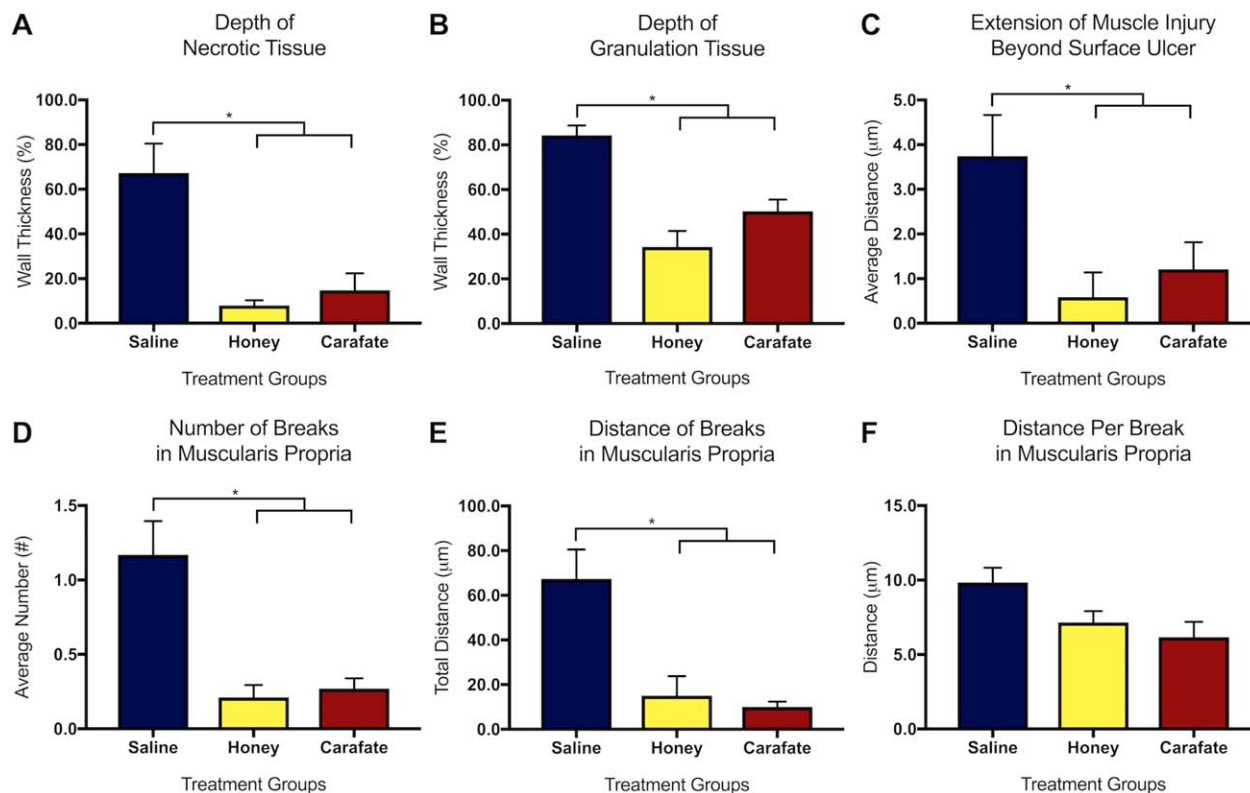


Fig. 5. The injury site on the porcine proximal esophagus was resected  $7 \pm 0.5$  days following button battery exposure, fixed in 10% formalin for  $\geq 24$  hours, and serially sectioned to 5-mm thickness (5–10 sections per animal). Slides from each section were stained with hematoxylin and eosin. Six outcomes were used to assess the injury. Observed in the control group was significantly greater depths of (A) necrosis and (B) granulation tissue (both extending to the adventitia, the deepest tissue layer), (C) spread of deep injury, and (D–F) loss of muscular integrity. Measurements were obtained using an ocular micrometer ( $n = 2, 3,$  and  $4$  for honey, Carafate<sup>®</sup>, and saline, respectively). Data are shown as mean  $\pm$  standard error of the mean.  $*P < .05$ . [Color figure can be viewed in the online issue, which is available at [www.laryngoscope.com](http://www.laryngoscope.com).]

issues, esophageal perforation, fistulization into adjacent structures (e.g., the trachea or major vessels), mediastinitis, spondylodiscitis, or even death from sepsis or exsanguination.<sup>1,5</sup> This is highlighted by an animal in the control group that experienced a complete esophageal perforation in close proximity to major vessels and embedment of the necrotic debris in the prevertebral fascia (Fig. 7C,D). Chronic or long-term complications can include esophageal stricture and dysphagia symptoms that require endoscopic dilations or esophagectomy for treatment. In some cases, tracheostomy and/or gastrostomy tube insertion, or other surgical interventions, may be required.

The orientation of anodic pole of the BB in the esophagus during an ingestion crisis directly impacts the resultant clinical pathologies because the anode-cathode junction, where the circuit closes on contact with the tissue, resides on that face. The ensuing reaction becomes evident within minutes of its placement on the tissue with visualization of hydrogen gas bubbling around the rim of the BB both in vitro and in vivo. The hydroxide-mediated injury was validated in the control group by the rapid rise in tissue pH, which was measured over time in vitro and confirmed in vivo at the conclusion of the experiment.

Our previous work with cadaveric porcine esophagus demonstrated the potential benefit of using weakly acidic solutions like lemon juice before BB removal and 0.25% acetic acid immediately following removal on this alkaline injury, and allayed fears of an exothermic reaction occurring as a result of pH neutralization. However, the primary injury already occurred with the 0.25% acetic acid protocol, and the unpalatability of lemon juice posed a high barrier to overcome in children.

This study focused on: 1) intervention during the golden window to prevent injury from occurring, 2) using higher viscosity acidic fluids to not only harness the benefit of pH neutralization but also create a protective barrier between the mucosa and the BB, and 3) ensuring these mitigating solutions were palatable options.

Honey is a sweet-tasting, viscous, weak acid found in most households, and Carafate<sup>®</sup> suspension is a weakly acidic, Food and Drug Administration–approved, cherry-flavored duodenal ulcer prescription known for its mucosal protective effects. As illustrated in vitro and in vivo, both are superior to other similarly weak acids at neutralizing the tissue pH and mitigating injury to a significant degree. Mechanistically, honey provides additional protection by acting as a physical barrier given its high viscosity. Carafate<sup>®</sup> may confer the same benefit

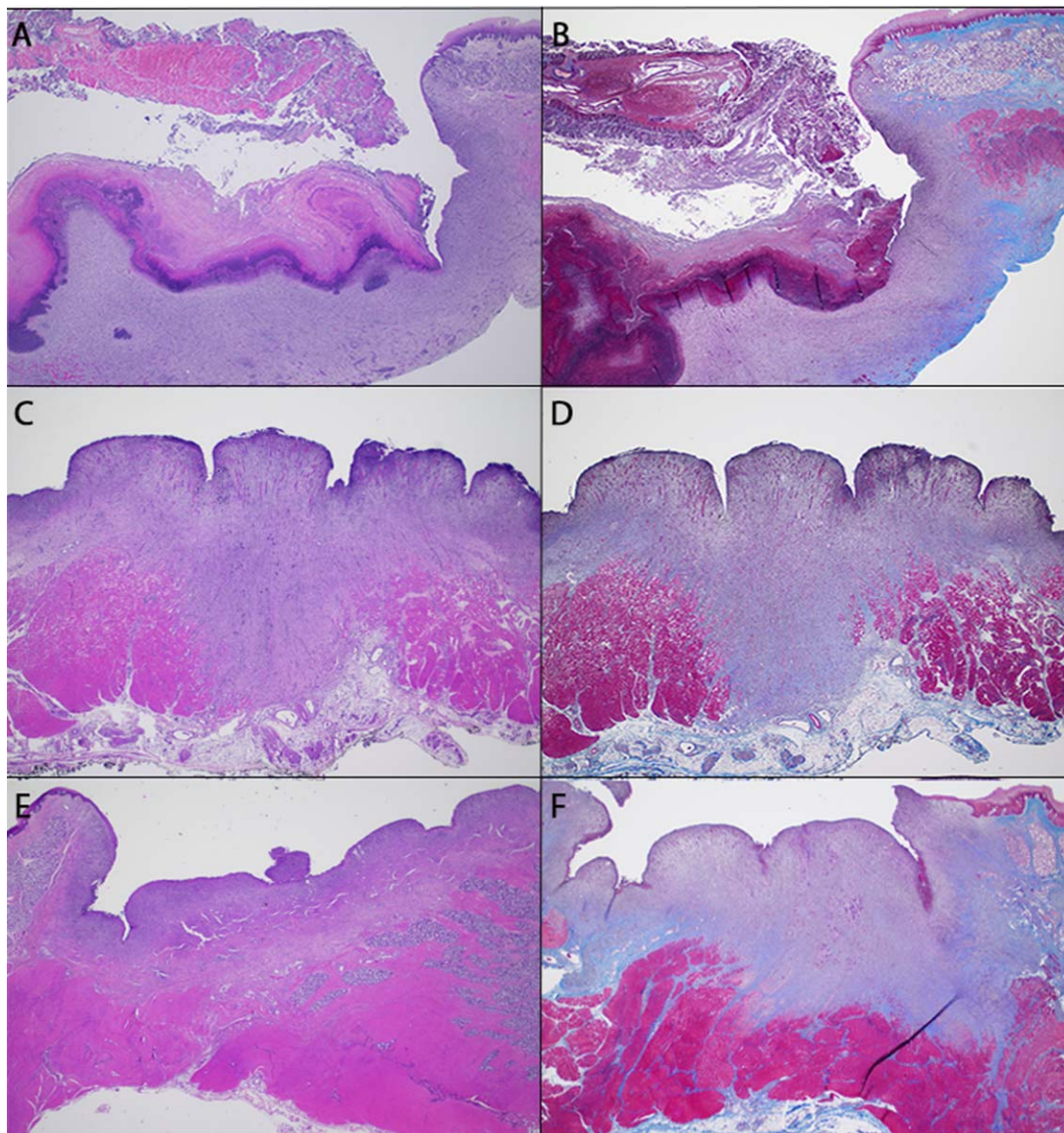


Fig. 6. For the saline-treated tissue, (A) hematoxylin and eosin (HE), 10×, (B) Masson's Trichrome (MT), 10×. Section of esophageal wall showing full-thickness coagulative necrosis of the muscularis propria (MP) and extending to underlying adventitia. Extensive granulation tissue underlying the necrosis is composed predominantly of inflammatory cells and loose collagen. For the honey-treated tissue, (C) HE, 10×, (D) MT, 10×. Section of esophageal wall with prominent granulation tissue and a focal break in the underlying MP. Relatively higher density of collagen deposition within this area of muscle damage and lack of damage to the underlying adventitia. For the Carafate<sup>®</sup>-treated tissue, (E) HE, 10×, (F) MT, 10x. Section of esophageal wall with prominent granulation tissue extending into the MP. Higher density of collagen deposition, where the granulation tissue meets the muscle and in between the muscle bundles. [Color figure can be viewed in the online issue, which is available at [www.laryngoscope.com](http://www.laryngoscope.com).]

when a BB augments the tissue microenvironment and the surface mucosa begins to ulcerate. Carafate<sup>®</sup> cross-links in acidic environments, forming a paste-like material.<sup>8</sup> This might be possible in the focal acidic microenvironments that develop near the cathode, allowing Carafate<sup>®</sup> to enhance its barrier function and slow electrical conduction.<sup>9</sup> Furthermore, Carafate<sup>®</sup> is negatively charged and binds to positively charged proteins and extracellular matrix components exposed in ulcerated tissue, protecting it from further injury.<sup>10</sup>

Complications are more likely to occur when nothing is done to mitigate a BB ingestion prior to its

removal, as demonstrated by the gross and histological analysis. Observed in the control group was a significantly greater extent of necrosis, loss of muscular integrity, and spread of injury as well as a decrease in reparative collagen deposition and a higher incidence of perforations. This severe injury pattern, only seen in the controls, was emphasized further on analysis of this group by its perforating and nonperforating subtypes.

These findings suggest an underlying mechanism for perforation development; extensive injury in the adjacent deep muscle beyond the small surface ulcer margins (exhibited by the NPC) leads to structural



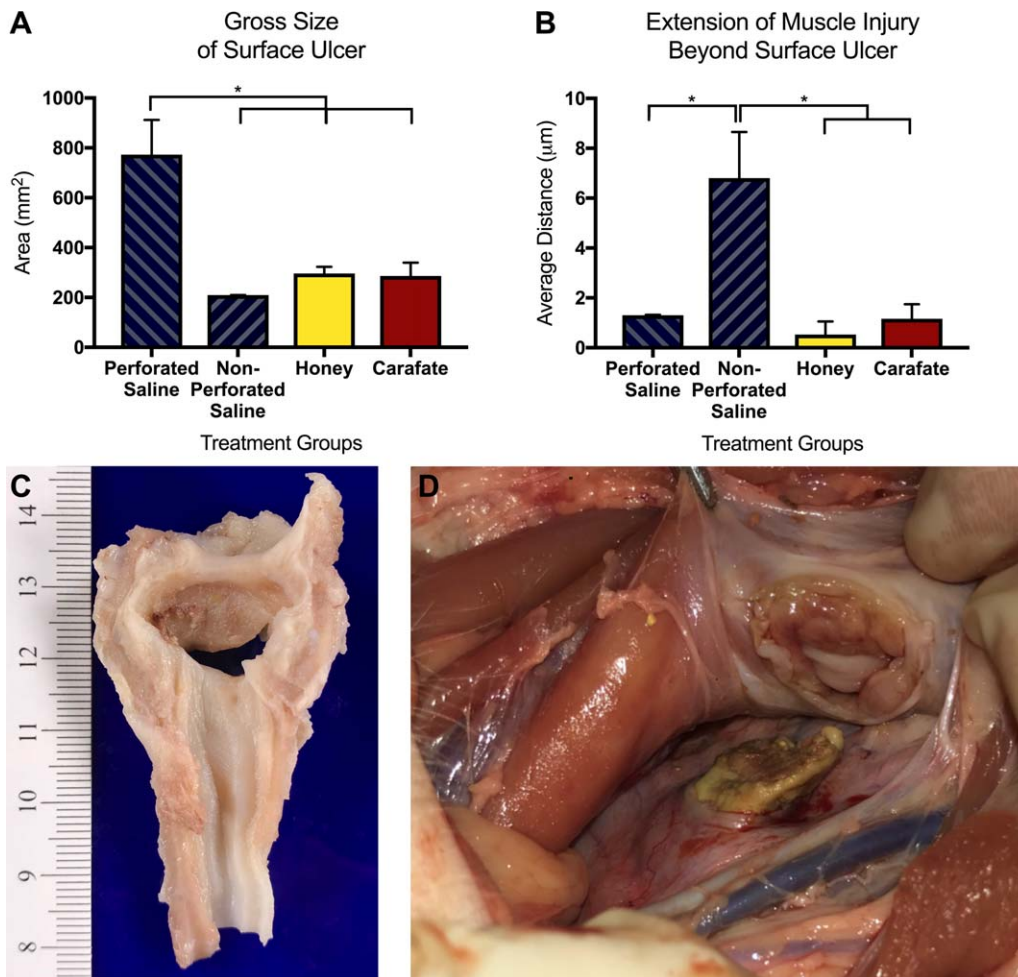


Fig. 7. Because perforations were seen only in the saline-treated controls, the gross analysis and histologic assessment by hematoxylin and eosin (HE) was redone examining the control by its perforating (PC) and nonperforating (NPC) subgroups. (A) Surface ulcer size and (B) outward extension of muscular injury highlight a possible mechanism for perforation development; extensive injury to the muscularis propria beyond the small ulcerative margins (seen in the NPC) leads to structural failure in a tissue region greater than the area of initial ulceration, resulting in surprisingly large perforations with minimal injury extension (seen in the PC). By comparison, an altogether different injury pattern—small ulcerations with minimal injury extension—is seen with use of honey or Carafate<sup>®</sup>, proving their effectiveness at blunting the injury process. Shown are gross images of a delayed perforation in the esophageal and diverticular walls that developed in one control animal within 60 minutes. (C) A large perforation (red arrow) is shown. (D) Embedment of the necrotic tissue in the prevertebral fascia and the proximity of the injury to the major vessels is appreciated. Measurements were obtained using a ruler or ocular micrometer.  $n = 2$  for the perforated and nonperforated saline controls ( $n = 3$  for Carafate<sup>®</sup>). Data are shown as mean  $\pm$  standard error of the mean.  $*P < .05$ . [Color figure can be viewed in the online issue, which is available at [www.laryngoscope.com](http://www.laryngoscope.com).]

failure in a tissue region greater than the area of initial ulceration, resulting in surprisingly large perforations with minimal outward extension of the deep muscle injury (demonstrated by the PC).

Taken as a whole, this study highlights the increased risk the control group has for developing perforating injuries, and other severe complications, from a BB insult. In comparison, honey and Carafate<sup>®</sup> were effective at blunting injury progression by changing the injury pattern to a more favorable one. Both treatments conferred protection against deep tissue damage, focally below the surface ulcer as well as beyond its margins, and by enabling a more robust healing response in areas of severe injury.

Thus, our suggestion would be to support an early-stage BB ingestion protocol of either honey or Carafate<sup>®</sup>

contingent upon the child's clinical picture. Caution against use should be exercised in cases of delayed diagnosis or late-stage ingestions, where clinical suspicion of perforation, mediastinitis, or sepsis already exists. Additionally, a history of contraindicated medical conditions, including severe allergy to honey or Carafate<sup>®</sup> and the age of the child if less than 1 year due to the small risk for infant botulism associated with honey, should be considered prior to initiating treatment.<sup>11</sup>

A standardized dosing volume and frequency that fell within physiologic range of saliva production and gastric capacity for young children was utilized for all solutions in this study to allow for direct comparative analysis.<sup>12,13</sup> It is possible that increasing irrigation frequency (e.g., 5–10 mL every 5 minutes) may enhance treatment efficacy, but further study of these intervals

are needed. Though future studies may help establish the ideal volume and frequency for each treatment, our current findings serve as a reasonable benchmark for clinical recommendations (10 mL = 2 teaspoons every 10 minutes), as realistically the intake limits will vary by child. The honey option is meant for home use and meant to be utilized until a child can get to a health care facility; once at a healthcare facility, Carafate® can be utilized until BB removal can occur. Nevertheless, it is important to understand that safely ingesting any amount of these mitigation solutions, prior to when BB removal can occur, is better than doing nothing from an intervention perspective.

Another point to consider is that Carafate® works best in environments with a pH of less than 4, as opposed to the alkaline environment at the BB injury site. Future work optimizing the efficacy of this medicinal compound in higher pH environments might be worthwhile. Alternatively, a new ideal beverage could be designed or identified. Regardless, the goals would be to reduce dosage size and frequency, neutralize highly alkaline tissue, create a contact barrier between the BB and esophageal tissue, and/or block battery discharge entirely.

Although an appealing concept for injury reduction, ingestion of pH-neutralizing viscous liquids prior to emergent endoscopic BB removal would contradict the established preoperative nothing by mouth (NPO) guidelines required for most pediatric surgeries to reduce the risk of gastric content aspiration under anesthesia.<sup>14,15</sup> However, the general consensus is that the risk is very low, particularly with the rapid sequence intubation techniques used in non-NPO emergent cases, and occurrences typically are benign.<sup>16–21</sup> Even for elective cases, there are trends toward reduced preoperative fasting times and inclusion of preoperative oral carbohydrate loading protocols.<sup>17,18,22,23</sup> Accordingly, it is our opinion that the greater risks associated with the rapidly progressing BB injury outweigh the lesser risks of aspiration-related anesthetic complications.

## CONCLUSION

Esophageal BB impactions are serious, conferring a high risk of debilitating complications and even death. Our cadaveric and live animal studies support that early intervention with honey or Carafate® suspension is clearly better than doing nothing. Thus, for witnessed or suspected early-stage BB ingestions, mitigation protocols with protective pH-neutralizing viscous solutions like honey in a home setting or Carafate® in the clinical setting have the potential to significantly slow the rate of esophageal injury prior to endoscopic removal, and should be considered in the algorithm for BB management.

## Acknowledgments

The authors gratefully acknowledge Michael Herron (sales executive) and Joan Canty (conventions department) from

KARL STORZ Endoscopy-America, Inc. for technical support and equipment procurement, respectively; Children's Hospital of Philadelphia's Department of Veterinary Resources, including Dr. Travis Seymour and the entire Large Animal Facility staff in the Abramson Research Center; and Children's Hospital of Philadelphia's Pathology Core Services and its staff, in particular Dan Martinez, Neena Panackel, Socrates Agrio-Oreilly, Joon Jung, and Elizabeth Tomesk.

## BIBLIOGRAPHY

- Litovitz T, Whitaker N, Clark L, White NC, Marsolek M. Emerging battery-ingestion hazard: clinical implications. *Pediatrics* 2010;125:1168–1177.
- The National Poison Data System. Button battery ingestion statistics. Available at: <http://www.poisson.org/battery/stats.asp>. Accessed February 2, 2018.
- Litovitz T, Whitaker N, Clark L. Preventing battery ingestions: an analysis of 8648 cases. *Pediatrics* 2010;125:1178–1183.
- Jatana KR, Rhoades K, Milkovich S, Jacobs IN. Basic mechanism of button battery ingestion injuries and novel mitigation strategies after diagnosis and removal. *Laryngoscope* 2017;127:1276–1282.
- Jatana KR, Litovitz T, Reilly JS, Koltai PJ, Rider G, Jacobs IN. Pediatric button battery injuries: 2013 task force update. *Int J Pediatr Otorhinolaryngol* 2013;77:1392–1399.
- Rivera EA, Maves MD. Effects of neutralizing agents on esophageal burns caused by disc batteries. *Ann Otol Rhinol Laryngol* 1987;96:362–366.
- National Capital Poison Center. NBIH button battery ingestion triage and treatment guideline. Available at: <https://www.poisson.org/battery/guideline>. Accessed February 1, 2018.
- Brogden RN, Heel RC, Speight TM, Avery GS. Sucralfate. A review of its pharmacodynamic properties and therapeutic use in peptic ulcer disease. *Drugs* 1984;27:194–209.
- Volker J, Volker C, Schendzielorz P, et al. Pathophysiology of esophageal impairment due to button battery ingestion. *Int J Pediatr Otorhinolaryngol* 2017;100:77–85.
- Nagashima R. Mechanisms of action of sucralfate. *J Clin Gastroenterol* 1981;3(suppl 2):117–127.
- Koriorh T. Simple remedies often best for common colds in young children. American Academy of Pediatrics website. Available at: <http://www.aapublications.org/content/32/12/32.5>. Accessed February 1, 2018.
- Watanabe S, Ohnishi M, Imai K, Kawano E, Igarashi S. Estimation of the total saliva volume produced per day in five-year-old children. *Arch Oral Biol* 1995;40:781–782.
- Moules T, Ramsay J. *The Textbook of Children's Nursing: Part 1*. Cheltenham, United Kingdom: Nelson Thornes Ltd.; 1998.
- Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: an updated report by the American Society of Anesthesiologists Task Force on Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration. *Anesthesiology* 2017;126:376–393.
- Smith I, Kranke P, Murat I, et al. Perioperative fasting in adults and children: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol* 2011;28:556–569.
- Kelly CJ, Walker RW. Perioperative pulmonary aspiration is infrequent and low risk in pediatric anesthetic practice. *Paediatr Anaesth* 2015;25:36–43.
- Andersson H, Zaren B, Frykholm P. Low incidence of pulmonary aspiration in children allowed intake of clear fluids until called to the operating suite. *Paediatr Anaesth* 2015;25:770–777.
- Mesbah A, Thomas M. Preoperative fasting in children. *BJA Educ* 2017;17:346–350.
- Neuhaus D, Schmitz A, Gerber A, Weiss M. Controlled rapid sequence induction and intubation—an analysis of 1001 children. *Paediatr Anaesth* 2013;23:734–740.
- Johr M. Anaesthesia for the child with a full stomach. *Curr Opin Anaesthesiol* 2007;20:201–203.
- Gencorelli FJ, Fields RG, Litman RS. Complications during rapid sequence induction of general anesthesia in children: a benchmark study. *Paediatr Anaesth* 2010;20:421–424.
- Muhly WT, Stricker PA. Preoperative fasting in children: is there room for improvement? *Paediatr Anaesth* 2017;27:791–792.
- Smith MD, McCall J, Plank L, Herbison GP, Soop M, Nygren J. Preoperative carbohydrate treatment for enhancing recovery after elective surgery. *Cochrane Database Syst Rev* 2014(8):CD009161.