

## AUTHORS

**Nathan Link, MD**, Fellow, Pediatric Emergency Medicine, University of New Mexico, School of Medicine, Albuquerque

**Jeffrey Bullard-Berent, MD, FAAP, FACEP**, Professor, Emergency Medicine and Pediatrics; Medical Director, Child Ready Virtual Pediatrics Department, University of New Mexico, School of Medicine, Albuquerque

## PEER REVIEWER

**Jennifer N. Chalam, MD, FAAP**, University of South Alabama School of Medicine, Mobile

## STATEMENT OF FINANCIAL DISCLOSURE

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## What Is Really BRUEing?

*In May 2016, the American Academy of Pediatrics (AAP) published clinical practice guidelines titled Brief Resolved Unexplained Events (Formerly Apparent Life-Threatening Events) and Evaluation of Lower-Risk Infants, suggesting a new terminology, an evaluation based on the risk of recurrent events or serious underlying causes, and key action statements (management recommendations) for patients meeting the brief resolved unexplained events (BRUE) definition for lower-risk patients. The authors review and discuss the definitions and key management strategies recommended in these new guidelines.*

— Ann M. Dietrich, MD, FAAP, FACEP

The death of any infant or child is horrifying. When that death cannot be explained, the family and medical community struggle for hope and understanding: hope that we can blame the child's demise on something, anything, and an understanding that will allow us an opportunity for prevention or successful intervention in future occurrences for other children.

### Apparent Life-threatening Event

In the late 1960s, a definition was put forth to describe these unexplained infant deaths: sudden infant death syndrome (SIDS). In 1991, SIDS, also known as crib death or cot death, was redefined as “the sudden death of an infant younger than one year of age, which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history.”<sup>1,2</sup>

“Unexplained” remains the critical portion of this definition, leaving those clinicians frustrated asking, “What was different about this infant? How can we identify and stratify this child who died from all the other children who have had scary or apparently life-threatening events but survived?” The term “near-miss SIDS” described those survivors until 1986, when the National Institutes of Health Consensus Conference on Infantile Apnea suggested the term apparent life-threatening event (ALTE) as an alternative.<sup>3</sup>

The term ALTE encompassed a group of children who survived an event “that is frightening to the observer and that is characterized by some combination of apnea (central or occasionally obstructive), color change (usually cyanotic or pallid but occasionally erythematous or plethoric), marked change in muscle tone (usually marked limpness), choking, or gagging. In some cases, the observer fears that the infant has died.”<sup>4</sup> Using “frightening” in its definition and “life-threatening” in its moniker, ALTE is both a challenging clinical diagnosis and much too easy a disposition for clinicians; a child experiencing any event that scary or that suggests an imminent death must be admitted.

In many respects, with a diagnosis of ALTE, the physician abrogated the responsibility of a thorough history, physical exam, and assessment. Providers are taught that the diagnosis is in the history. Although certainly not the intent, the use of the

## EXECUTIVE SUMMARY

- Brief resolved unexplained events (BRUE) describe events occurring in children younger than 1 year of age, observed to have a less than one-minute episode that has resolved completely, and includes one or more of the following: cyanosis or pallor; absent, decreased, or irregular breathing; marked change in tone (hypertonia or hypotonia); altered level of responsiveness.
- In an American Academy of Pediatrics (AAP) guideline, BRUE replaced the term apparent life-threatening event (ALTE), and allows for more precise identification of events that likely are related to normal physiologic responses (periodic breathing of the newborn, breath-holding spells, gastroesophageal reflux) vs. those that suggest a true pathology (hemodynamic instability, central apnea).
- The diagnosis of BRUE is made only when the cause of the event is unexplained, after a thorough history and physical examination.
- An event that occurs in the setting of a changing or concerning history, a child who is older than 1 year of age, episodes that lasts for more than one minute, abnormal vital signs (including a history of fever) at the time of examination, and/or other findings on history or exam that suggest an explanation (e.g., history of gagging or choking suggesting gastroesophageal reflux, bleeding, bruising, abnormal growth, respiratory distress, etc.) excludes the diagnosis of BRUE.
- The AAP policy statement lists pulmonary infection (bronchiolitis, pneumonia, croup, and upper respiratory infections), urinary tract infection, sepsis, meningitis, gastroenteritis, viral syndrome, and other specific organisms (pertussis, respiratory syncytial virus, respiratory virus) as part of the BRUE differential diagnosis.
- The inborn errors of metabolism present with acute or chronic encephalopathy, typically manifested by lethargy, poor feeding, apnea, tachycardia, and recurrent vomiting. Mitochondrial disorders present with neurologic symptoms: muscle weakness, hypotonia, peripheral neuropathy, ataxia, ptosis, bulbar signs, spasticity, stroke-like events, tremor, dystonia, seizures, and myoclonus.
- The differential diagnosis of BRUE includes abusive head trauma, caregiver-fabricated illness (known as Munchausen by proxy or medical child abuse), poisoning, intentional suffocation, and medical neglect.

term ALTE allowed providers to settle for the surface history without delving for the details. A somewhat concerning history and normal exam did not change the provider's disposition, as the caregiver's experience was paramount. Even considering the differential diagnosis for these events (cardiac, pulmonary, neurologic, gastrointestinal, infectious, metabolic, non-accidental trauma), providers recognized the infant in front of them was unlikely to have any of those. Yet, how could providers expect the worried parent or caregiver to accept a diagnosis of ALTE and not test and admit his/her child? Simple lab tests and X-rays might make the family and the providers feel more confident. Could caregivers or providers really sleep if this child was discharged with no further investigation?

Despite its name, ALTE rarely is the harbinger of devastating illness. However, its diagnosis has led to unneeded laboratory and imaging studies, as well as therapeutic monitoring and interventions.

### Brief Resolved Unexplained Events

In May 2016, the AAP published its first clinical practice guidelines relating to infants who experienced an ALTE.<sup>5</sup> These guidelines, titled *Brief Resolved Unexplained Events (Formerly Apparent*

*Life-Threatening Events) and Evaluation of Lower-Risk Infants*, suggest a new terminology, evaluation based on risk of recurrent events or serious underlying causes, and key action statements (management recommendations) for patients meeting the brief resolved unexplained events definition for lower-risk patients.

The evidence-based guidelines were based on a comprehensive review of the ALTE literature from 1970 to 2014, and aimed to improve patient care and outcomes, as well as reduce unnecessary and expensive medical interventions, all the while encouraging a patient- and family-centered decision-making process. This article will review these guidelines using cases to clarify diagnosis and management recommendations. In this age of exotic coffees and beers, many search for newer and better brews, but for patients and families, this is what's BRUEing: brief resolved unexplained events.

### BRUE Defined

BRUE describes an event occurring in a child younger than 1 year of age, observed to have a less than one-minute episode that has completely resolved, and includes one or more of the following:

- cyanosis or pallor;
- absent, decreased, or irregular breathing;

- marked change in tone (hyper- or hypotonia);
- altered level of responsiveness.

Similar to the SIDS definition, the diagnosis of BRUE is made only when the cause of the event is unexplained, after a thorough history and physical examination. Unlike SIDS, BRUE does not require an exhaustive workup or autopsy for diagnosis.

### Cases

**Case 1:** A 12-week-old male born at 37 weeks by spontaneous vaginal delivery presents with his mother, who reports that soon after breastfeeding, he had an episode consisting of 30 seconds of perioral cyanosis and diminished respirations. She called 911, and the patient was brought to the emergency department (ED) by ambulance. Emergency medical services (EMS) reports that the patient did not have any episodes of cyanosis during transport, but they placed him on 1 L oxygen by nasal cannula. The mother says she is worried he damaged his lungs and may have suffered brain damage during the episode. She is now afraid to breast-feed him. On physical exam, you note:

- Pulse (P): 134, respiratory rate (RR): 32, blood pressure (BP): 74/46 mmHg, oxygen saturation (O<sub>2</sub> sat): 100% on

1 L room air, temperature (T): 37.1° C by rectal thermometer;

- General: well-appearing, interactive infant with normal skin color; moving upper and lower extremities;
- HEENT (head, eyes, ears, nose, and throat): normocephalic and atraumatic, oropharynx without ulcers or discoloration;
- Skin: no rashes or bruising;
- Cardiovascular (CV): regular rate and rhythm, no murmurs;
- Respiratory (Resp): clear to auscultation in all lung fields;
- Abdominal (Abd): soft, non-tender, no palpable organomegaly;
- Musculoskeletal (MSK): good tone in upper and lower extremities bilaterally;
- Neurological (Neuro): good muscle tone.

Does this patient meet BRUE criteria? He is younger than a year old, had an episode of altered respirations with perioral cyanosis that resolved in less than one minute, and has returned to baseline. Therefore, this event qualifies as a BRUE.

**Case 2:** A 4-month-old female born at 35 weeks by cesarean delivery secondary to preeclampsia presents with a 20-second episode of turning red in the face after her 4-year-old brother put a lemon wedge in her mouth. The father was watching them and left the kitchen for a moment, returning to find his daughter reddening in the face with the lemon wedge on the floor. He picked her up and she turned red while crying. This lasted one minute. The patient then stopped crying and her face returned to normal color. The father brought her to the ED, and is worried the lemon may have burned her mouth. On physical exam, you note the following:

- P: 128, RR: 34, BP: 78/41 mmHg, O<sub>2</sub> sat: 96% on room air, T: 36.8° C by rectal thermometer;
- General: well-appearing, interactive infant with normal skin color; moving upper and lower extremities;
- HEENT: normocephalic and atraumatic, oropharynx without ulcers or discoloration;
- Skin: no rashes or bruising;
- CV: regular rate and rhythm, no murmurs;
- Resp: clear to auscultation in all fields;
- Abd: soft, non-tender, no palpable organomegaly;
- MSK: good tone in upper and lower extremities bilaterally;
- Neuro: good muscle tone.

**Table 1. Distinguishing Characteristics Between ALTE and BRUE**

|                                   | ALTE                           | BRUE  |
|-----------------------------------|--------------------------------|---|
| Age                               | No restriction                 | < 1 year  |
| Duration                          | Not applicable                 | < 1 minute  |
| Color                             | Any color change               | Only cyanosis or pallor   |
| Tone                              | Any change in tone             | Change in tone, specifically hypotonia or hypertonia              |
| Breathing                         | Apnea (central or obstructive) | Absent, decreased, irregular                                      |
| Events associated with swallowing | Choking or gagging             | Choking, gagging, spitting up, and vomiting specifically excluded |
| Level of responsiveness           | Not applicable                 | Altered during episode, now at baseline                           |
| Threat identifier                 | Observer/caretaker             | Provider  |

Does this patient meet the criteria for BRUE? The patient has some of the elements of BRUE (younger than 1 year of age; brief, resolved event), but there was no cyanosis or pallor, no changes in respiration, no altered tone, and no altered level of alertness. An infant turning red in the face can be part of a normal physiologic response and, therefore, does not qualify as a BRUE. In addition, this event is explained by her big brother putting a lemon in her mouth. With the benefit of a clear preceding event, as well as her turning red rather than blue or pallid, she does not meet BRUE criteria.

### Exclusion Criteria

Exclusion criteria for BRUE are categorized by history, age, duration, vital signs, and apparent explanations found within the history and physical exam. An event that occurs in the setting of a changing or concerning history in a child who is older than 1 year that lasts for more than one minute, has abnormal vital signs (including a history of fever) at the time of examination, and/or other findings on history or exam that suggest an explanation (e.g., history of gagging or choking suggesting gastroesophageal reflux, bleeding, bruising, abnormal growth, respiratory distress, etc.) excludes the diagnosis of BRUE.

### BRUE vs. ALTE

At first glance, the differences between BRUE and ALTE may seem subtle, but the AAP policy work group has drawn

very specific distinctions.<sup>6</sup> ALTE does not have a defining age group, whereas BRUE is specifically for children younger than 1 year of age. BRUE defines an event as being completely resolved, but the ALTE diagnosis allows for patients to be symptomatic or asymptomatic on presentation to the clinician. This distinction also is apparent when considering the “unexplained” definition inherent in BRUE. If a patient has signs or symptoms on exam that suggest an explanation, he/she does not have BRUE.

BRUE also changes the emphasis from the caregiver’s perceptions to that of the clinician’s characterizations. A color change of any kind is a characteristic of ALTE, but in BRUE the only relevant color change is either cyanosis or pallor. Turning red in the face does not meet criteria for BRUE. Respiratory events are defined as absent, diminished, or irregular in BRUE vs. only apnea for ALTE. Tonal changes are described more specifically in BRUE as hypotonia or hypertonia, rather than simply change in tone, as is true for ALTE. Gagging and choking are a central concept of ALTE but, from a BRUE perspective, suggest an explanation of gastroesophageal reflux or respiratory infection, and thus are not included. Altered level of responsiveness was added to the BRUE definition, as it may be helpful in distinguishing cardiac, respiratory, metabolic, or neurologic events but are not part of the ALTE definition. Cardiopulmonary resuscitation (CPR) administration by

caregivers was included in many of the definitions of ALTE, but BRUE emphasizes the clinician's characterizations of the reported event, and only includes CPR administration by trained medical providers. (See Table 1.)

## BRUE Risk Assessment

One critical aspect of the AAP subcommittee's systematic review was identifying children who met the definition of BRUE and had a low risk of having recurrent events or an underlying serious diagnosis. An evidence-based comprehensive review of the ALTE literature, in which each article was reviewed and scored by two committee members, found that patients who met the BRUE definition who were younger than 2 months of age, born at < 32 weeks' gestation (and < 45 weeks postconceptual age), had more than one event, and were at greater risk of adverse outcomes or serious diagnoses.

By defining these higher-risk encounters, the AAP subcommittee suggested a Lower Risk BRUE cohort as defined in Table 2.

**Case 3:** A 6-month-old female born at 38 weeks by spontaneous vaginal delivery presents to the ED after she developed perioral cyanosis, coughing, and increased work of breathing after feeding from a bottle and then being placed on her back. The mother picked up the infant immediately after the coughing episode, noted she was pale and limp, and called 911. The entire episode lasted approximately 45 seconds. When EMS arrived, the infant was back to her baseline. On further questioning, the mother reports similar but less severe events, multiple times over the last two months, and notes that the patient has a chronic cough. She reports that the baby frequently vomits with feeding. On physical exam you note:

- P: 144, RR: 37, BP: 81/47, O<sub>2</sub> sat: 99% on room air, T: 37.1° C by rectal thermometer;
- General: well-appearing, interactive infant with normal skin color; moving upper and lower extremities;
- HEENT: normocephalic and atraumatic, oropharynx without lesions;
- Skin: no rashes or bruising;
- CV: regular rate and rhythm, no murmurs;
- Respiratory: clear to auscultation in all lung fields;
- Abd: soft, non-tender, no palpable organomegaly;

## Table 2. Identification of Lower-risk BRUE

- Age > 60 days
- Prematurity: gestational age ≥ 32 weeks and postconceptional age ≥ 45 weeks
- First BRUE (no previous BRUE ever and not occurring in clusters)
- Duration of event < 1 minute
- No CPR by trained medical providers
- No concerning historical features
- No concerning physical examination findings

- MSK: good tone in upper and lower extremities bilaterally;
- Neuro: good muscle tone.

Does this patient meet criteria for BRUE? She is younger than 1 year of age, the event was brief and now resolved, and her exam is completely normal, suggesting the possibility of BRUE. However, the history suggests that this patient has had recurrent episodes associated with chronic cough and vomiting. The history suggests multiple possible explanations, including gastroesophageal reflux, aspiration, congenital heart disease, etc. This pertinent history rules out BRUE as a diagnosis.

If this child's history was one of recurrent episodes without associated symptoms of vomiting and cough, she would have been identified as a higher-risk BRUE. Of note, this case is based on a case report of an infant found to have a double aortic arch after presenting to the ED with a similar event.<sup>7</sup>

**Case 4:** A previously healthy, term 7-month-old male presents to the ED with his mother and grandmother. He awoke from a nap, smiled at his grandmother, and then he suddenly appeared "dazed and spaced out." His face turned pale and he did not respond to his grandmother. The grandmother called the mother who came in from another room and noted the pale color and unresponsiveness of the child. She initiated CPR with two rescue breaths, and the child cried immediately, quickly returning to his baseline. The entire event took 30-50 seconds. The family drove the child to the ED. Nothing like this had ever happened before. On physical exam, you note the following:

- P: 132, RR: 26, O<sub>2</sub> sat: 98% on room air, T: 37.0° C rectal thermometer;
- General: alert, active infant sitting solo and trying to crawl on the gurney;
- HEENT: atraumatic and normocephalic, nares patent without discharge, no oral lesions;

- Skin: no rashes or bruising noted;
- CV: regular rate and rhythm, no murmur, equal pulses throughout;
- Respiratory: clear to auscultation, no increased work of breathing;
- Abdomen: soft, non-tender, no masses
- MSK: full range of motion in all extremities, no deformity;
- Neurologic: awake, alert infant moving all extremities, deep tendon reflexes 2/4 at patella bilaterally; no clonus at the ankles noted.

What is your assessment of this patient? He is younger than 1 year of age, the event was less than a minute, and he returned to baseline quickly. This fits BRUE, but is he higher or lower risk? He is older than 2 months, term, this is the first event, the duration was less than one minute, he required no CPR by trained medical providers, and the history and physical exam do not reveal any concerning features. This event fulfills criteria for lower-risk BRUE.

The recognition of lower-risk BRUE patients is critical when implementing these practice guidelines, as key action statements or evidence-based management guidelines are described for this group only. The higher-risk BRUE stratification suggests patients who need further investigation and treatment, whereas the lower-risk BRUE group requires few, if any, interventions.

## Unexplained Does Not Mean Overlooked: The Importance of History and Physical Exam in BRUE

"Unexplained" is an uncomfortable word for caregivers and clinicians, especially when it is used to describe what was perceived by the caregiver or patient as a serious event. Practitioners recognize that aches, pains, and illness often have no identifiable cause, but we continue to strive to find answers and explain our

patients' maladies. How can it be that an unexplained event, as defined by BRUE, is better than a "real diagnosis"? As practitioners become more comfortable with the diagnosis of BRUE, we can share with our patients' families why "unexplained" is better than most of the alternatives. The differential diagnosis of BRUE is long and complex, including at least five organ systems, as well as genetic/metabolic, child maltreatment, infectious, and toxic causes. Understanding and considering this inexhaustive list is key to an effective history and physical exam, and ultimately to the stratification of BRUE to include lower risk and higher risk and the associated recommended key actions.<sup>5</sup>

The differential diagnosis of BRUE, both higher and lower risk, includes cardiovascular, gastrointestinal, neurologic, otolaryngologic, pulmonary, genetic/metabolic, infectious, toxic, and child maltreatment causes. The next section will describe these possible etiologies and the historical and physical exam findings that correlate with these diagnoses.

## Differential Diagnosis for BRUE

### Cardiovascular

The cardiovascular differential diagnosis for BRUE can be divided into structural disease (congenital heart disease, vascular ring/sling/compression, cardiomyopathy/myocarditis) and arrhythmogenic (channelopathies, ventricular pre-excitation, arrhythmia). The history of most of these will reveal recurrent or persistent episodes that may include cyanosis, pallor, difficulty feeding, difficulty breathing, irritability, fatigue, as well as a positional component to the child's distress. The physical exam may reveal cyanosis, increased work of breathing, diminished or differential pulses and blood pressure, murmur, tachycardia, bradycardia, or hepatosplenomegaly. The exam may be completely normal if an arrhythmogenic episode resolved prior to the exam.

### Gastrointestinal

The gastrointestinal system differential diagnosis includes swallowing difficulties (dysphagia/choking, esophageal dysmotility, laryngeal chemoreflex), gastroesophageal reflux (GER), obstruction (bowel obstruction, intussusception, esophageal foreign bodies), tracheoesophageal fistula (TEF), gastroenteritis, and

milk-soy-protein intolerance (MSPI).<sup>8</sup> A history of gagging, choking, or vomiting excludes the diagnosis of BRUE. Patients with GER typically have recurrent events of vomiting and, thus, are categorized as higher-risk BRUE. TEF typically presents with coughing, choking, difficulty feeding, or respiratory distress, which all tend to be recurrent. Gastroenteritis is diagnosed when both vomiting and diarrhea are part of the history. It would be unusual for patients with bowel obstruction or intussusception to present without a history of pain or vomiting. MSPI was not included in the defining article's differential diagnosis, but one recent article suggests this diagnosis in the higher-risk BRUE.

### Neurologic

The neurologic differential diagnoses that need to be considered with BRUE include space-occupying structural lesions (intracranial mass, intracranial hemorrhage, intracranial structural or vascular abnormalities, hydrocephalus), seizures, strokes, neuromuscular disorders, central hypoventilation syndrome, apnea of prematurity, demyelinating disorders (transverse myelitis, multiple sclerosis, acute disseminated encephalomyelitis), and infantile botulism. The history for space-occupying lesions can vary from slow and insidious (masses) to rapid and fulminate (bleeding arterial-vascular malformation). A seizure history may be quite subtle in infants and may be confused with normal infant actions (normal myoclonus, stooling, grimacing, normal reflux). Central hypoventilation and apnea of prematurity are characterized by breathing irregularities and cyanosis. Consideration of stroke, neuromuscular disorders, demyelinating disorders, and infantile botulism requires scrupulous physical exams, especially in the youngest patients.

### Otolaryngologic

Otolaryngologic structural issues must be considered in the evaluation of BRUE. Some are noted readily on external physical exam (maxillary hypoplasia, micrognathia, macroglossia), whereas others are suggested by history, but only demonstrated with internal exams (choanal atresia, pyriform aperture stenosis, laryngomalacia, subglottic stenosis tracheomalacia, and adenotonsillar hypertrophy). Choanal atresia and pyriform aperture stenosis present early in life with

cyanosis and feeding difficulty secondary to obstruction of the nasopharynx in obligate nose breathers of early infancy. Laryngomalacia, subglottic stenosis, and tracheomalacia typically present as noisy breathers who may have associated cyanosis, retractions, cough, and persistent or recurrent events. Adenotonsillar hypertrophy causing obstructive sleep apnea is more common in the 3- to 6-year-old age group, but can be seen in infants, often presenting with persistent snoring and/or poor weight gain. Stimulation of the pharynx/larynx through eating, coughing, GER, or foreign objects can trigger a vasovagal reflex suggesting a BRUE event. In these cases, the history of the event is essential, as the physical exam likely will be normal. Unintentional suffocation from bedding or co-sleeping always must be considered in SIDS presentations, but also should be considered in BRUE.

### Pulmonary

The pulmonary differential diagnoses to be considered in BRUE can be divided into intrinsic (asthma, congenital airway anomalies, hemorrhage) and extrinsic (aspiration, foreign body, infection). In most cases, all of these conditions are associated with a history of respiratory distress, cough, or noisy breathing prior to the event. Eliciting a history of noisy breathing prior to the event with a sudden worsening of symptoms suggests laryngotracheal malacia or subglottic stenosis being exacerbated by intercurrent infection. A history of mild nasal discharge preceding a choking/gagging event during feeding is a common presentation for parental concern, but does not meet BRUE criteria. Pulmonary hemorrhage presents rapidly, is rare in pediatrics, and usually is found in patients with cystic fibrosis or congenital heart disease. The physical exam usually is positive for increased work of breathing, wheeze, rhonchi, stridor, or nasal congestion in all of these conditions.

### Infectious

The AAP policy statement lists pulmonary infection (bronchiolitis, pneumonia, croup, and upper respiratory infections), urinary tract infection (UTI), sepsis, meningitis, gastroenteritis, viral syndrome, and other specific organisms (pertussis, respiratory syncytial virus [RSV], respiratory virus) as part of the BRUE differential

diagnosis. Most of these conditions are marked by fussiness, irritability, poor feeding, change in behavior, and fever. In younger or premature infants, these all may be absent or noted by caregivers only in retrospect. As pertussis and RSV can present with apnea, especially in the infants younger than 2 months of age, a history of cough may not be found. A previous history of UTI or genitourinary anomaly suggests the possibility of UTI. The infectious causes of a BRUE-type event require a focused physical exam. Inspection of the fontanelles, capillary refill, mucus membranes, and work of breathing are helpful in finding signs of meningitis, sepsis, respiratory infections, and/or dehydration from gastroenteritis.

### Genetic/Metabolic

The genetic/metabolic differential diagnosis for BRUE can be separated broadly into inborn errors of metabolism (IEM), including urea cycle, organic acidemia, fatty oxidation disorders, mitochondrial disorders, electrolyte disturbances, hypocalcemia, and hypoglycemia. The IEMs present with acute or chronic encephalopathy, typically manifested by lethargy, poor feeding, apnea, tachycardia, and recurrent vomiting. Mitochondrial disorders affect mitochondrial electron transport and, therefore, affect tissues with high energy needs. Most commonly, children with mitochondrial disorders present with neurologic symptoms: muscle weakness, hypotonia, peripheral neuropathy, ataxia, ptosis, bulbar signs, spasticity, stroke-like events, tremor, dystonia, seizures, and myoclonus. Twenty percent of children with mitochondrial disorders present with developmental delay or psychiatric issues, and 10% present with liver disease.<sup>9</sup>

Infants with electrolyte disturbances may have no symptoms. Usually electrolyte disturbances are caused by input or output issues and, thus, questions regarding an infant's feeding (how much, how often, what type), as well as urine and stool output, are essential. Hypocalcemia in infancy is separated into early (24–72 hours after birth) and late (a week to weeks after birth) presentations. Premature and low birth weight infants are at higher risk for hypocalcemia. Symptoms include irritability, jitteriness, poor feeding, tremors, lethargy, and seizures. Infants born to diabetic mothers, born prematurely, or born at low birth weight, very large birth weight, or

under stress are at risk for hypoglycemia. Including questions relevant to these issues is essential in the history of BRUE-type events. Typical symptoms of hypoglycemia include poor feeding, poor tone, lethargy, jitteriness, cyanosis, apnea, and seizures.

It would be unusual for any of the patients with underlying genetic or metabolic problems to have a completely normal exam after presentation for a BRUE-like event. However, quantifying decreased activity and poor tone takes careful observation and a skilled clinician when examining infants.

### Child Maltreatment

The differential diagnosis of BRUE includes abusive head trauma, caregiver-fabricated illness (known as Munchausen by proxy or medical child abuse), poisoning, intentional suffocation, and medical neglect. Unexplained, poorly explained, differently explained, alternatively explained, or explained but does not make developmental sense events all should raise the suspicion of child maltreatment. Probing and re-probing the time preceding the event, the event, the event resolution, and the after-effects of the event are critical for an accurate diagnosis of BRUE, but also in eliciting history that excludes BRUE. A physical exam focusing on signs of head trauma, eye findings, oral/nasal trauma (torn frenulum), musculoskeletal trauma, and integument exam looking for patterned rash or bruising in areas unexpected for a child of the given age is essential.

### Toxin Exposure

The AAP policy guideline for differential diagnosis of BRUE also includes medication adverse effects, substance exposure via human milk, environmental exposures, and vaccine reactions. Pain, redness, local swelling, or fever after vaccination may cause crying leading to a BRUE-like event. A history of medication use, including over-the-counter oral and topical medications, encourages further investigation and possible etiology for an event. Exposures through breast milk require a careful history, including the mother's history of substance abuse, narcotic use, and eating. Environmental exposures may be straightforward (i.e., using a barbecue to heat the house in winter causing carbon monoxide poisoning) or vague.

### Miscellaneous

Acrocyanosis, hypothermia, and breath-holding spells are in the differential diagnosis for BRUE. Acrocyanosis is a common finding in newborns and consists of peripheral cyanosis of the palms, soles, and lips. No central cyanosis accompanies the peripheral cyanosis of acrocyanosis, and it is caused by benign vasomotor changes that cause vasoconstriction. Hypothermia typically presents with decreased activity and poor feeding. Infants are at risk for hypothermia because of their large body surface area to weight ratio, inability to complain of being chilled, and inability to remedy their problem without others' help. Of note, hypothermia may be a cause of acrocyanosis. Breath-holding spells are most common in children 6 to 18 months of age. These episodes occur when the child is startled, angry, or injured and begins to cry. While crying, the child may hold his or her breath, may lose consciousness, and may have a seizure. These episodes are very upsetting to the caregiver, but a complete history typically elicits an inciting event.

**Case 5:** A 3-month-old male born at 35 weeks by spontaneous vaginal delivery presents to the ED with an episode of gagging and spitting up, resulting in a 20-second episode of "turning blue in the face" and diminished breathing. The mother placed the infant flat on a changing table soon after breastfeeding and then the infant spit up. The mother immediately picked up the infant, patted him on the back, and gave him some water from a bottle to help him "clear out his mouth." The infant cried after the 20-second cyanotic episode, after which his face returned to its normal color and he calmed down. The mother stayed with him at home for half an hour after the episode, but decided to come to the ED "just to have him checked out." On physical exam, you note:

- P: 131, RR: 34, BP: 77/51, O<sub>2</sub> sat: 97% on room air, T: 36.4° C by rectal thermometer;
- General: well-appearing, interactive infant with normal skin color; moving upper and lower extremities;
- HEENT: normocephalic and atraumatic, oropharynx without lesions;
- Skin: no rashes or bruising;
- CV: regular rate and rhythm, no murmurs;
- Resp: clear to auscultation in all fields;

**Table 3. History of Possible BRUE Event**

| Event           | General  | Just Prior to Event  | End of Event  | After Event  |
|-----------------|--|--|---|--|
| What            | Describe the event   | Awake, asleep, eating, feeding, choking, etc.?   | Parent intervention: picked up, back blows, CPR, or stopped on its own? | Back to baseline? Parent intervention: child offered food or drink? 911 called?          |
| Who             | Witnesses, reporters?  | Witnesses?   | Witnesses?  | Medical providers on site?   |
| When            | Date, time, relationship to eating, sleeping, defecating, urinating? | Abrupt or gradual onset?   | Abrupt or gradual end? Duration of event?                               | How long until back to baseline? How soon after event did patient arrive for evaluation? |
| Where           | Home, daycare, other; what was the child's positioning?              | Were choking or suffocating objects nearby?  | Remained at original site of event?                                     |  |
| Other questions |  | Making noise?<br>Active/moving vs. quiet/flaccid?<br>Conscious/responsive?<br>Tone increased/decreased?<br>Repetitive movements?<br>Distressed/alarmed?<br>Breathing: yes/no/distress?<br>Skin: normal, pale, red, blue?<br>Bleeding?<br>Lips: normal, pale, blue? |   |  |

- Abd: soft, non-tender, no palpable organomegaly;
- MSK: good tone in upper and lower extremities bilaterally;
- Neuro: good muscle tone.

Does this patient fit the definition of BRUE? Although the episode was brief, resulted in cyanosis, and decreased respirations, the definition of BRUE excludes gagging or choking episodes associated with spitting up or vomiting. Underlying conditions such as GER or infectious gastroenteritis are far more likely to cause spitting up or vomiting. Therefore, these symptoms warrant alternative diagnostic workup, management, and treatment.

**Case 6:** A 7-month-old female twin born at 34 weeks by spontaneous vaginal delivery presents to the ED with her parents after a 40-second episode of perioral cyanosis that occurred yesterday while in the father's care. The father reports that he was caring for the twins who were in their crib when he saw the infant suddenly turn blue in the face. He picked her up and she was limp in his arms, but her facial cyanosis quickly resolved and the patient

"woke up" crying. Since then, the patient has been fussy and seems uninterested in feeding. On physical exam, you note:

- P: 146, RR: 37, BP: 79/44, O<sub>2</sub> sat: 96% on room air, T 36.6° C by rectal thermometer;
- General: well-appearing, interactive infant with normal skin color;
- HEENT: normocephalic, atraumatic with a flat anterior fontanelle, oropharynx with upper lip frenulum bruising;
- Skin: bruises noted on shins and thighs;
- CV: regular rate and rhythm, no murmurs;
- Resp: clear to auscultation in all lung fields;
- Abd: soft, non-tender, no palpable organomegaly;
- MSK: swelling noted on left lower extremity around bruising;
- Neuro: good muscle tone.

You ask the parents about the bruising on her lower extremities, and the father says she's been cruising around the house and bumping into furniture. Does this infant meet the criteria for BRUE? The

episode fits the definition of BRUE, but a 7-month-old with multiple bruises and swelling of the lower extremity and a story inconsistent with developmental milestones raises concern for non-accidental trauma. The delay in seeking care also is of concern and requires further inquiry. The history and physical exam findings place this patient in the higher-risk BRUE category, and this child warrants a workup evaluating specifically for non-accidental trauma.

### Focused History and Physical Exam for BRUE

The original AAP policy statement also includes a detailed list of historical and physical features to be considered in the evaluation of potential BRUE.<sup>5</sup> (*See Tables 3, 4, and 5*). By definition, lower-risk BRUE patients must have no concerning history or physical findings. Since lower-risk BRUE is a diagnosis of exclusion, taking the time to explore the history and physical exam fully is essential.

**Case 7:** A 10-month-old male born term by repeat caesarean delivery presents

after he choked on a grape at home, resulting in 50 seconds of apnea and facial cyanosis. His grandmother, a retired pediatric nurse, administered an abdominal thrust that dislodged the grape, and two rescue breaths, after which the patient started crying spontaneously. The infant required several minutes to calm down, but then returned to his baseline. As soon as the patient was calm, the grandmother brought him to the ED for evaluation. On physical exam, you note:

- P: 131, RR: 34, BP: 77/51, O<sub>2</sub> sat: 97% on room air, T: 36.7° C by rectal thermometer;
- General: well-appearing, interactive infant moving upper and lower extremities;
- HEENT: normocephalic and atraumatic, oropharynx without lesions;
- Skin: no rashes or bruising;
- CV: regular rate and rhythm, no murmurs;
- Resp: clear to auscultation in all lung fields;
- Abd: soft, non-tender, no palpable organomegaly, area of redness just inferior to xiphoid process;
- MSK: good tone in upper and lower extremities bilaterally;
- Neuro: good muscle tone.

Does this patient meet the definition of BRUE? He had an obvious precipitating factor to his episode after aspirating a grape that required abdominal thrusts to dislodge. This is not a BRUE because of the known choking episode that caused the event.

**Case 8:** A 9-month-old female born at 36 weeks by spontaneous vaginal delivery presents to the ED after she had 15 seconds of perioral cyanosis after her mother dropped a glass, which shattered and appeared to startle her. The mother reports the infant tensed when the glass hit the ground and did not appear to take a breath during the 15 seconds. Immediately following the episode, the child began to cry and returned to her baseline within two minutes. The mother rushed her to the ED to make sure she wasn't injured or didn't have a seizure.

On physical exam, you note:

- P: 124, RR: 28, BP: 83/46, O<sub>2</sub> sat: 96% on room air, T: 36.2° C by rectal thermometer;
- General: well-appearing, interactive infant with normal skin color; moving upper and lower extremities;
- HEENT: normocephalic and

**Table 4. Past Medical History to Explore in Possible BRUE**

|                                       |   |
|---------------------------------------|---|
| Recent History                        | Illness in preceding days? If yes, details on the signs and symptoms  |
| Past Medical History                  | Pre-perinatal history, gestational age, newborn screen, previous episodes, gastroesophageal reflux, breathing problems (noisy, snoring), growth and development, illness, injuries or other emergencies, hospitalizations, surgeries, immunizations (when?), medications (including oral and topical over-the-counter), allergies   |
| Family History                        | Sudden family deaths < 35 years of age and in infancy? BRUE/ALTE in sibling, long QT, arrhythmia, inborn errors of metabolism, genetic, developmental delay in family?  |
| Social History/ Environmental History | Family structure, who lives at home? Housing general condition, water damage, mold? Exposure to tobacco smoke, toxic substances, or drugs? Illness exposures? Support system? Caregiver level of concern? Impact if child requires hospitalization? Previous child protective services or police encounters? Exposure to adults with substance abuse or mental health issues? |
| Child Maltreatment                    | Changing versions of the history? Inconsistency with child's developmental stage? Unexplained bruising? Incongruence between caregivers' expectations and child's developmental age, including assigning negative attributes to the child   |

atraumatic, oropharynx without lesions;

- Skin: no rashes or bruising;
- CV: regular rate and rhythm, no murmurs;
- Resp: clear to auscultation in all lung fields;
- Abd: soft, non-tender, no palpable organomegaly;
- MSK: good tone in upper and lower extremities bilaterally;
- Neuro: good muscle tone.

Does this patient meet the definition of BRUE, and if so, what risk classification does she fit? She is an infant younger than 1 year of age, and her episode lasted less than one minute and included cyanosis, making this a BRUE. She is older than 60 days, she was born ≥ 32 weeks' gestation, and her corrected gestational age is ≥ 45 weeks. She did not receive CPR by a trained medical provider, this was the first such event, and her history and physical exam are unremarkable. This case illustrates a lower-risk BRUE. However, the essential point of BRUE is "unexplained," and this patient's detailed history suggests an answer. The child was startled by a falling glass, tensed, and did

not breathe for a few seconds. This history clearly suggests a breath-holding spell, and, thus, does not meet BRUE criteria.

**Key Action Statements:  
Management Recommendation for Lower-risk BRUE**

The objectives of this first AAP policy statement on BRUE (formerly known as ALTE) were to define BRUE and use this new term to replace ALTE, to provide an approach to find a population at lower risk for recurrent episodes or serious underlying pathology, and, finally, to provide management recommendations for these defined lower-risk patients. The guideline recommendations follow the AAP Steering Committee on Quality Improvement and Management, Classifying Recommendation for Clinical Practice Guidelines.<sup>1</sup> Recommendations are graded as strong, moderate, or weak based on quality of evidence and the balance of benefits vs. harms. A recommendation statement of "should" or "should not" is associated with strong or moderate recommendations. "May" or "need not" recommendation statements are

**Table 5. Focused Physical Exam for BRUE**

| System             | Findings   |
|--------------------|--|
| General appearance | <ul style="list-style-type: none"> <li>• Craniofacial abnormalities (mandible, maxilla, nasal)</li> <li>• Responsiveness to environment</li> </ul>   |
| Growth             | <ul style="list-style-type: none"> <li>• Length</li> <li>• Weight</li> <li>• Head circumference</li> </ul>   |
| Vital signs        | <ul style="list-style-type: none"> <li>• Temperature</li> <li>• Respiratory rate</li> <li>• Heart rate</li> <li>• Blood pressure</li> <li>• Oxygen saturation</li> </ul>   |
| Integument         | <ul style="list-style-type: none"> <li>• Color</li> <li>• Perfusion</li> <li>• Injury/intact</li> <li>• Bruising in unusual locations for developmental age</li> </ul>   |
| Head               | <ul style="list-style-type: none"> <li>• Shape</li> <li>• Fontanelles</li> <li>• Ecchymosis</li> <li>• Injury</li> </ul>   |
| Eyes               | <ul style="list-style-type: none"> <li>• Extraocular movements</li> <li>• Pupillary response</li> <li>• Conjunctival hemorrhage</li> <li>• Retinal hemorrhage</li> </ul>   |
| Nose and mouth     | <ul style="list-style-type: none"> <li>• Blood in nares</li> <li>• Blood in mouth</li> <li>• Trauma or obstruction</li> <li>• Torn frenulum</li> </ul>   |
| Neck               | <ul style="list-style-type: none"> <li>• Mobility</li> </ul>   |
| Chest              | <ul style="list-style-type: none"> <li>• Auscultation (rhonchi, rales, stridor, wheeze)</li> <li>• Palpation for rib tenderness and crepitus</li> </ul>  |
| Heart              | <ul style="list-style-type: none"> <li>• Rhythm</li> <li>• Rate</li> <li>• Auscultation</li> <li>• Pulses</li> <li>• Capillary refill</li> </ul>   |
| Abdomen            | <ul style="list-style-type: none"> <li>• Organomegaly</li> <li>• Masses</li> <li>• Distention</li> <li>• Tenderness</li> </ul>   |
| Genitalia          | <ul style="list-style-type: none"> <li>• Bleeding</li> <li>• Bruising</li> <li>• Any abnormalities</li> </ul>  |
| Extremities        | <ul style="list-style-type: none"> <li>• Muscle tone</li> <li>• Injuries</li> <li>• Limb deformities consistent with fractures</li> </ul>  |
| Neurologic         | <ul style="list-style-type: none"> <li>• Alertness/responsiveness</li> <li>• Responds to sound and visual stimulation</li> <li>• Symmetry of movement/tone and strength</li> <li>• General tone</li> <li>• Symmetric reflexes</li> </ul> |

associated with weak recommendations.

The Key Action Statements address eight areas of concern for lower-risk BRUE patients: cardiopulmonary, child abuse, neurology, infectious diseases, gastroenterology, inborn errors of metabolism, anemia, and patient- and family-centered care. (See Table 6.)

### Case 1 Revisited

A 12-week-old male born at 37 weeks by spontaneous vaginal delivery presents to the ED with his mother who reports he had an episode soon after breastfeeding consisting of 30 seconds of perioral cyanosis and diminished respirations. She called 911 and the child was brought to the ED by ambulance. EMS placed the patient on oxygen for transport because of the history of cyanosis and poor respiratory effort. The mother says she is worried the baby damaged his lungs and may have suffered brain damage during the episode, and is scared to breastfeed him. On physical exam, you note the following:

- P: 134, RR: 32, BP: 74/46, O<sub>2</sub> sat: 100% on 1 L, T: 36.8° C by rectal thermometer;
- General: well-appearing, interactive infant with normal skin color; moving upper and lower extremities;
- HEENT: normocephalic and the anterior fontanelle is flat and not bulging, oropharynx without ulcers or discoloration;
- Skin: no rashes or bruising;
- CV: regular rate and rhythm, no murmurs;
- Resp: clear to auscultation in all lung fields;
- Abd: soft, non-tender, no palpable organomegaly;
- MSK: good tone in upper and lower extremities bilaterally;
- Neuro: good muscle tone.

How would you approach the workup for this patient? How would you counsel the patient's mother? The BRUE clinical practice guidelines provide an evidence-based approach to identifying whether this infant has a lower risk of a clinically significant condition that caused the event. The patient in Case 1 is younger than 1 year of age, had an episode of altered respirations with perioral cyanosis that resolved in less than one minute, and has returned to baseline. Therefore, this event qualifies as a BRUE. The next step in assessing this patient presentation is

**Table 6. BRUE Management Recommendations for Lower-risk Patients**

| Should  | Should Not  |
|---|---|
| <ul style="list-style-type: none"> <li>• Provide education to caregivers about BRUEs</li> <li>• Engage caregivers in shared decision-making to develop a mutually satisfactory plan for evaluation, disposition, and follow-up</li> </ul> | <ul style="list-style-type: none"> <li>• Obtain labs including complete blood count, blood culture, chemistry, blood gases, metabolic evaluation (serum amino acids, urine organic acids)</li> <li>• Obtain imaging studies including chest X-ray, echocardiogram, electroencephalogram</li> <li>• Obtain studies for gastroesophageal reflux</li> <li>• Facilitate home cardiac and respiratory monitoring</li> <li>• Prescribe acid suppression or antiepileptic therapies</li> </ul> |
| May   | Need Not  |
| <ul style="list-style-type: none"> <li>• Obtain 12-lead ECG</li> <li>• Test for pertussis</li> <li>• Monitor patients in the ED with continuous pulse oximetry and serial observations for &lt; 4 hours</li> </ul>                        | <ul style="list-style-type: none"> <li>• Obtain viral respiratory testing, urinalysis, blood glucose, serum bicarbonate, serum lactate, or neuroimaging</li> <li>• Admit the patient solely or inpatient cardiac and pulse oximetry monitoring</li> </ul>   |

determining the risk classification.

The BRUE risk classification algorithm used a systematic review of ALTE<sup>12</sup> to identify factors that conferred lower risk to infants who experience an event. The following elements identify an infant as lower risk after a BRUE: age > 60 days, if history of prematurity then gestational age ≥ 32 weeks and postconceptional age ≥ 45 weeks, first BRUE (no history of a previous BRUE, or cluster of BRUE), duration of event less than one minute, no CPR performed by trained medical provider, no concerning historical features, and no concerning physical examination findings. If any of these criteria are not met, then the patient is in the higher risk category and warrants further workup based on the presentation of the BRUE.

Based on the BRUE risk classification, the patient qualifies as low risk; however, on further questioning, the mother reports that she had a daughter who drowned at 5 years of age and a nephew who died unexpectedly in his sleep at 7 years of age. She is afraid that her infant son also will die.

Multiple unexplained deaths of first relatives are concerning for a cardiac channelopathy, such as long QT or Brugada syndrome. Therefore, the patient is classified as a higher-risk BRUE, warranting further workup. Using the BRUE definition and the lower-risk BRUE criteria and focusing on detailed history and physical examinations supports the clinician in making sound judgments.

## Summary

The recent AAP Policy guideline *Brief Resolved Unexplained Events (Formerly Apparent Life-Threatening Events) and Evaluation of Lower-Risk Infants* was created to define BRUE and changes the terminology of ALTE to BRUE, to provide a risk-based approach to identify patients at risk for recurrent events or serious underlying disorders, and finally to provide management recommendations for low-risk BRUE patients.

The BRUE guidelines are intended to alleviate parent concern, minimize unnecessary medical interventions, and improve patient outcomes by identifying patients at low risk for clinically significant causes of an event. A meta-analysis of 12 studies between 1970-2017 with 3,005 patients with ALTE found comparable risk of death for infants after a low-risk BRUE and the baseline infant mortality rate in the United States,<sup>11</sup> supporting the utility of the BRUE algorithm to identify lower-risk patients.

In the guideline, BRUE replaces the term ALTE, and allows for more precise identification of events that are likely related to normal physiologic responses (periodic breathing of the newborn, breath-holding spells, gastroesophageal reflux) vs. those that suggest a true pathology (hemodynamic instability, central apnea).

By diagnosing an infant with a BRUE, clinicians can eliminate unnecessary testing that exposes infants to unnecessary risk, better use limited hospital resources to serve sicker patients, and engage in

shared decision-making with parents and caretakers, thereby minimizing stress associated with ED visits for both patients and caretakers.

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## CME/CE Questions

1. What is a key difference between the definition of apparent life-threatening event (ALTE) and brief resolved unexplained event (BRUE)?
  - a. ALTE has no age restriction while BRUE requires age < 1 year.
  - b. ALTE has no duration restriction while BRUE requires event < 1 minute.
  - c. ALTE allows for any color change while BRUE only allows for cyanosis or pallor.
  - d. All of the above
2. According to the BRUE guidelines, what should providers always do when working up a potential BRUE?
  - a. Engage the infant's caregivers to develop a plan of evaluation.
  - b. Monitor infant in the ED for up to four hours.
  - c. Discharge infant with home cardiac and pulse oximetry monitoring.
  - d. Obtain viral respiratory swab to rule out viral cause of BRUE.
3. Which of the following is *not* part of the BRUE risk classification?
  - a. Age > 60 days
  - b. Born ≥ 32 weeks gestation and corrected gestational age ≥ 45 weeks
  - c. No CPR performed on the infant
  - d. First BRUE with no past history of previous BRUE
4. Which of the following patients qualifies as a BRUE?
  - a. An 8-month-old female with fever to 38.6° C presenting with rigors lasting for 45 seconds and diminished respirations during the episode, but who is now back to baseline
  - b. A 3-month-old male born at 40 weeks' gestation presenting after episode of stiffening for 30

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- seconds immediately after waking up in his crib
  - c. A 3-month-old male born at 39 weeks' gestation presents after developing perioral cyanosis following a choking episode during bottle feeding and who is now back to baseline
  - d. An 11-month-old female with four days of nasal congestion and cough presenting after 40 seconds of increased work of breathing, who is now back to baseline
5. Which of the following qualifies as a lower-risk BRUE?
  - a. A 7-week-old male born at 39 weeks' gestation presents after becoming pale and stiff for 35 seconds 10 minutes after breastfeeding and now is back to baseline.
  - b. A 4-month-old female presents after a first episode of apnea that lasted 25 seconds, and is now back to baseline. The infant cries with palpation of left lower extremity, and she is found to have a spiral tibial fracture on that side.
  - c. A 9-month-old female presents to the ED for the second time this month for an episode of stiffening and pallor. The first episode lasted 30 seconds, and the second episode lasted 40 seconds. The infant returned to baseline after each episode, but it took approximately 15 minutes to recover each time.
  - d. A 7-month-old male presents to the ED after his mother had difficulty waking him up from a nap to breastfeed. Mom reports he was lethargic for approximately 40 seconds, became pale, cried vigorously, and then refused to feed for several minutes.
6. Which of the following is *not* a diagnostic criterion for BRUE?
  - a. Cyanosis or pallor
  - b. Hyper- or hypotonia
  - c. Return to baseline level of health within five minutes of event
  - d. Altered level of responsiveness
7. According to the BRUE guidelines, when gastroesophageal reflux (GER) is suspected as the cause of an episode of apnea with cyanosis lasting less than one minute in an infant, what should the clinician do?
  - a. Prescribe a trial of ranitidine and have patient follow-up with primary care provider.
  - b. Refer the patient to a pediatric gastroenterologist.
  - c. Recommend burping the infant midway through feeding and keeping the infant upright for 30 minutes following a feed.
  - d. The BRUE guidelines do not apply to GER.
8. Which of the following is *not* a goal of the BRUE guideline?
  - a. Provide standardized diagnostic protocols for low- and high-risk BRUE.
  - b. Eliminate unnecessary testing that exposes infants to unnecessary risk.
  - c. Better use limited hospital resources to serve sicker patients.
  - d. Minimize stress for patients and caretakers.

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