



Brief resolved unexplained events: a new diagnosis, with implications for evaluation and management

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Abstract

Brief resolved unexplained events (BRUE) are concerning episodes of short duration (typically < 1 min) characterized by a change in breathing, consciousness, muscle tone (hyper- or hypotonia), and/or skin color (cyanosis or pallor). The episodes occur in a normal-appearing infant in the first year of life, self-resolve, and have no readily identifiable explanation for the cause of the event. Previously called apparent life-threatening events (ALTE), the term BRUE was first defined by the American Academy of Pediatrics (AAP) in 2016. The criteria for BRUE carry greater specificity compared to that of ALTE and additionally are indicative of a diagnosis of exclusion. While most patients with BRUE will have a benign clinical course, important etiologies, including airway, cardiac, gastrointestinal, genetic, infectious, neurologic, and traumatic conditions (including nonaccidental), must be carefully considered. A BRUE is classified as either lower- or higher-risk based on patient age, corrected gestational age, event duration, number of events, and performance of cardiopulmonary resuscitation at the scene. The AAP clinical practice guideline provides recommendations for the management of lower-risk BRUEs, advocating against routine admission, blood testing, and imaging for infants with these events, though a short period of observation and/or an electrocardiogram may be advisable. While guidance exists for higher-risk BRUE, more data are required to better identify proportions and risk factors for serious outcomes among these patients.

Conclusion: BRUE is a diagnosis with greater specificity relative to prior definitions and is now a diagnosis of exclusion. Additional research is needed, particularly in the evaluation of higher-risk events. Recent data suggest that the AAP guidelines for the management of lower-risk infants can be safely implemented. This review article summarizes the history, definitional changes, current guideline recommendations, and future research needs for BRUE.

What is Known:

- BRUE, first described in 2016, is a diagnosis used to describe a well-appearing infant who presents with change in breathing, consciousness, muscle tone (hyper- or hypotonia), and/or skin color (cyanosis or pallor).
- BRUE can be divided into higher- and lower-risk events. Guidelines have been published for lower-risk events, with expert recommendations for higher-risk BRUE.

What is New:

- BRUE carries a low rate of serious diagnoses (< 5%), with the most common representing seizures and airway abnormalities.
- Prior BRUE events are associated with serious diagnoses and episode recurrence.

Keywords Brief · Resolved · Unexplained event · Apparent life-threatening event · Pallor · Practice guideline

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Abbreviations

AAP	American Academy of Pediatrics
ALTE	Apparent life-threatening event
BRUE	Brief resolved unexplained event
CPG	Clinical practice guideline
CPR	Cardiopulmonary resuscitation
ED	Emergency department
SIDS	Sudden infant death syndrome
SUPC	Sudden unexpected postnatal collapse

Introduction

The pediatrician is frequently required to assess an infant following an episode characterized by changes in mental status, coloration, abnormal movements, and/or breathing. The terminology and criteria used for such events have undergone progressive refinement over the last four decades. The current nomenclature, called brief resolved unexplained events (BRUE), was described in 2016 by the American Academy of Pediatrics (AAP) subcommittee on apparent life-threatening events (ALTE). BRUE carries greater specificity and is a diagnosis of exclusion compared to prior definitions [1]. The published clinical practice guideline (CPG) by the AAP risk stratifies patients and provides suggestions for the management of lower-risk patients [1]. Though the term was introduced by a professional society based in the USA, these definitions have since been reported in journals and professional societies from other countries [2–6]. In this review, we summarize the history, terminology, current research, and management guidelines of BRUE.

Definition of BRUE

BRUE applies to well-appearing infants who present following a brief (< 1 min) episode characterized by one or more of the following: cyanosis or pallor, change in muscle tone (increased or decreased), change in responsiveness, and absent, irregular, or decreased breathing [1]. The definition should be applied when there is no other explanation for a qualifying event after conducting a complete history and examination.

In the CPG, these events are classified as either lower- or higher-risk [1]. An event is classified as higher-risk if there are concerns identified during the historical or physical examination, such as a family history of sudden cardiac death, non-diagnostic social, feeding or respiratory problems, or any of the following: age \leq 60 days, prematurity (born < 32 weeks gestation) with a corrected gestational age of fewer than 45 weeks, performance of cardiopulmonary resuscitation (CPR) by a trained medical provider, event

duration greater than one minute, and/or more than one lifetime episode (including multiple events prior to clinical presentation or further separated in time).

History

BRUE represents the latest in a line of iterative definition changes which have corresponded with changes in the understanding of the pathophysiology of these events. Due to initial concerns about a correlation between transient episodes reported by caregivers and sudden infant death syndrome (SIDS), these events were initially called “near miss SIDS” or “aborted crib deaths” [7–9].

To avoid a “potentially misleadingly close association” between these spells and SIDS, the National Institutes of Health Consensus Development Conference on Infantile Apnea and Home Monitoring in 1987 coined the term apparent life-threatening event (ALTE). ALTE was defined as an episode “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” [10]. The report acknowledged that ALTE could occur secondary to other conditions but continued to raise concern regarding an association between ALTE and mortality. Despite associative evidence suggesting that as many as 11% of SIDS events may be preceded by ALTE [11], prospective [12, 13] and retrospective [14–16] studies have suggested that SIDS and ALTE are likely distinct conditions.

The BRUE CPG authors provide several reasons for the updated terminology. The committee felt that the definition required additional precision in order to justify clinical decisions (i.e., hospital admission, diagnostic testing). ALTE in comparison is a nonspecific diagnosis with heterogeneous etiologies, varying from the relatively benign (gastroesophageal reflux) to severe (abusive head trauma.) The use of a more straightforward definition may decrease variation and improve quality of care. Additionally, there was a need to remove the term “life-threatening” from the definition, to avoid reinforcing caregiver perceptions about the potential severity of the event [1].

ALTE and BRUE differ in important ways. Unlike ALTE, BRUE is restricted to infants less than 1 year of age. BRUE is a diagnosis of exclusion made after a thorough history and physical examination. For example, a child with findings consistent for gastroesophageal reflux presenting with a reflux event occurring immediately prior to an observed change in respiration would meet criteria for ALTE but not BRUE. Events such as gagging do not fit under the criterion for BRUE. The “color change” which fits under the BRUE

Table 1 Application of brief resolved unexplained event (BRUE) criteria to apparent life-threatening events (ALTE)

Author (year)	Type	Setting	Years	N	Key findings
Meyer [17]	Retrospective	Admitted patients	2013–2016	87 with ALTE	20 (23%) with BRUE; 95% higher-risk
Nosetti [19]	Prospective survey	Referrals to sleep center	2016	32 with ALTE	26 (81%) with BRUE; 62% higher-risk
Colombo [20]	Retrospective	Admitted patients	2006–2016	84 with ALTE	49 (58%) with BRUE; 67% higher-risk
Ramgopal [18]	Secondary analysis of prospective registry	Emergency department	1997–2007	762 with ALTE	326 (43%) with BRUE; 79% higher-risk
Gerber [21]	Retrospective	Emergency department	2013–2015	78 with ALTE	1 (1%) with BRUE, higher-risk
DeLaroche [22]	Retrospective	Emergency department	2010–2016	3325 patients with a diagnosis code relevant to BRUE	98 (3%) with BRUE; 90% higher-risk

definition does not include redness. Importantly, the BRUE definition requires the child to be well-appearing on presentation; this is not required in the ALTE definition [1, 10].

Investigators have attempted to retrospectively classify ALTE events to see how many would fit into the new rubric of BRUE. Several single-center studies have noted widely varying Figs. (1–81%) of patients diagnosed with ALTE who meet BRUE criteria (Table 1) [17–22]. Most patients with ALTE who may now be classified with BRUE fit into the higher-risk group.

BRUE from a European perspective

An international consensus has not been reached on BRUE. In the UK, the term BRUE, with its updated definition, has not yet formally been accepted by the Royal College of Paediatrics and Child Health, although the college's journal has published a review of the term [3]. Health boards have also begun advocating that BRUE should replace ALTE and additionally suggest patients be risk stratified into lower- and higher-risk groups [23].

In other parts of Europe, the reception to the new guidelines has been more nuanced, with some advocating for use of both terms. In a guideline update, the Italian Pediatrics Society advocated for retaining ALTE and using BRUE for the subset of patients with “mild, idiopathic” events as defined by the AAP CPG [6, 24]. A similar approach has been advocated by other European experts [24].

Recent attention within Europe has also been given to sudden unexpected postnatal collapse (SUPC), a term used to describe a newborn of greater than 35 weeks gestational age, with a normal APGAR score at 10 min, and otherwise considered healthy, who presents with cardiorespiratory collapse within the first few days of life (up to 1 week) [25,

26]. As these patients are ill-appearing at presentation, such patients would not meet criteria for BRUE.

BRUE as a sentinel event for serious disease

Prospective research on BRUE has been limited and is challenging because of its heterogenous nature. Given that only a minority of ALTE events fit into the current definition of BRUE [17–21], the applicability of prior outcomes research for ALTE to BRUE is limited [27, 28]. A meta-analysis which attempted to calculate the risk of mortality 4 months after a BRUE event, derived from studies on ALTE, calculated this risk to be 1 in 800 [29], though this is likely high, given the challenging nature of identifying BRUE cases from nonspecific ALTE events [30]. Retrospective studies which generally have attempted to retroactively apply BRUE criteria to ALTE have suggested that BRUE can be associated with later development of language delays, trauma, infections, genetic disorders, seizure disorders, child abuse, sleep apnea, and recurrent events [18, 20, 22, 31].

A prior prospective study by Bonkowsky et al. provides some evidence for risk assessment of patients with BRUE [32]. This study included patients from birth to 12 months of age with ALTE but specifically excluded patients with a known past medical history or with an obvious diagnosis made by the emergency department (ED) or admitting doctor. By following a narrower inclusion criterion, this cohort is comparable to patients with BRUE. In a longitudinal assessment of 471 patients followed over a mean of 5.1 years, two (0.4%) died of chronic epilepsy. Significant diagnoses included child abuse (11%), epilepsy (4%), and developmental delay (3%) [32].

A retrospective cohort study from 15 pediatric and community hospitals used a multifaceted inclusion approach to

provide more recent data on the serious outcomes among patients with BRUE [33]. This study, which included 2,036 patients with BRUE, found serious diagnoses in 82 (4%). Nearly half (45%) were made after the index hospital visit. The most common serious diagnoses in this cohort included seizures ($n=23$, 1%), airway abnormalities ($n=13$, <1%), and abusive head trauma ($n=7$, <1%). Applying the higher- and lower-risk stratification criteria to this cohort demonstrated a negative predictive value of 90% and a positive predictive value of 23%. Among all patients in the study (those discharged from the ED or those admitted), a history of a similar event was associated with a risk of underlying serious diagnosis, recurrent event, or a revisit.

Initial assessment

In order to characterize patients with BRUE, the infant must be well-appearing (with normal vital signs), have at least one of the four defining criteria for BRUE, and not have a finding on history or physical examination that is consistent with an alternative diagnosis [1]. Once a BRUE is diagnosed, the provider should classify the patient as lower- or higher-risk. A suggested guideline, derived from the CPG and from our local implementation, is provided in Fig. 1.

The history and physical examination should be focused on identifying potential alternative diagnoses and applying risk stratification [1]. A description of the event includes the number of events, location (at home or elsewhere) timing, preceding events, duration, what exact alterations occurred, and if the event occurred during wakefulness or sleep. The provider should clarify if there was choking or gagging, if the baby had repetitive movements, color changes (particularly of the lips), and relation to last feeding. The event termination should be described, including if it was sudden or gradual and if abortive activities (such as blowing or tapping) were performed. If CPR was performed, the physician should determine if it was performed by a trained CPR provider. A recent history should be clarified, including injuries or illnesses. A thorough past medical history should include a perinatal history, gestational age, newborn screening results, history of noisy breathing, prior hospitalizations, developmental status, and medications used. A family history should include sudden unexplained deaths in the family, BRUE-like episodes in siblings, dysrhythmias (including long QT syndrome), and inborn errors of metabolism. A social history should include data with respect to housing, exposure to environmental toxins (including tobacco), number of residents in the home, caregivers, level of concern, and previous involvement with child protective services. A changing history, unexplained bruising, and an incongruence between the caregiver's expectations and a child's developmental stage should raise concern for child abuse.

Physical examination should include vital signs, growth for age, an assessment of the child's general appearance, color, and perfusion. A child abuse exam should include an evaluation for any bruising, deformities, torn frenulum, and a retinal exam, if indicated. An evaluation for infection should include an assessment for fever and for any focal evidence of disease, such as respiratory conditions.

Management

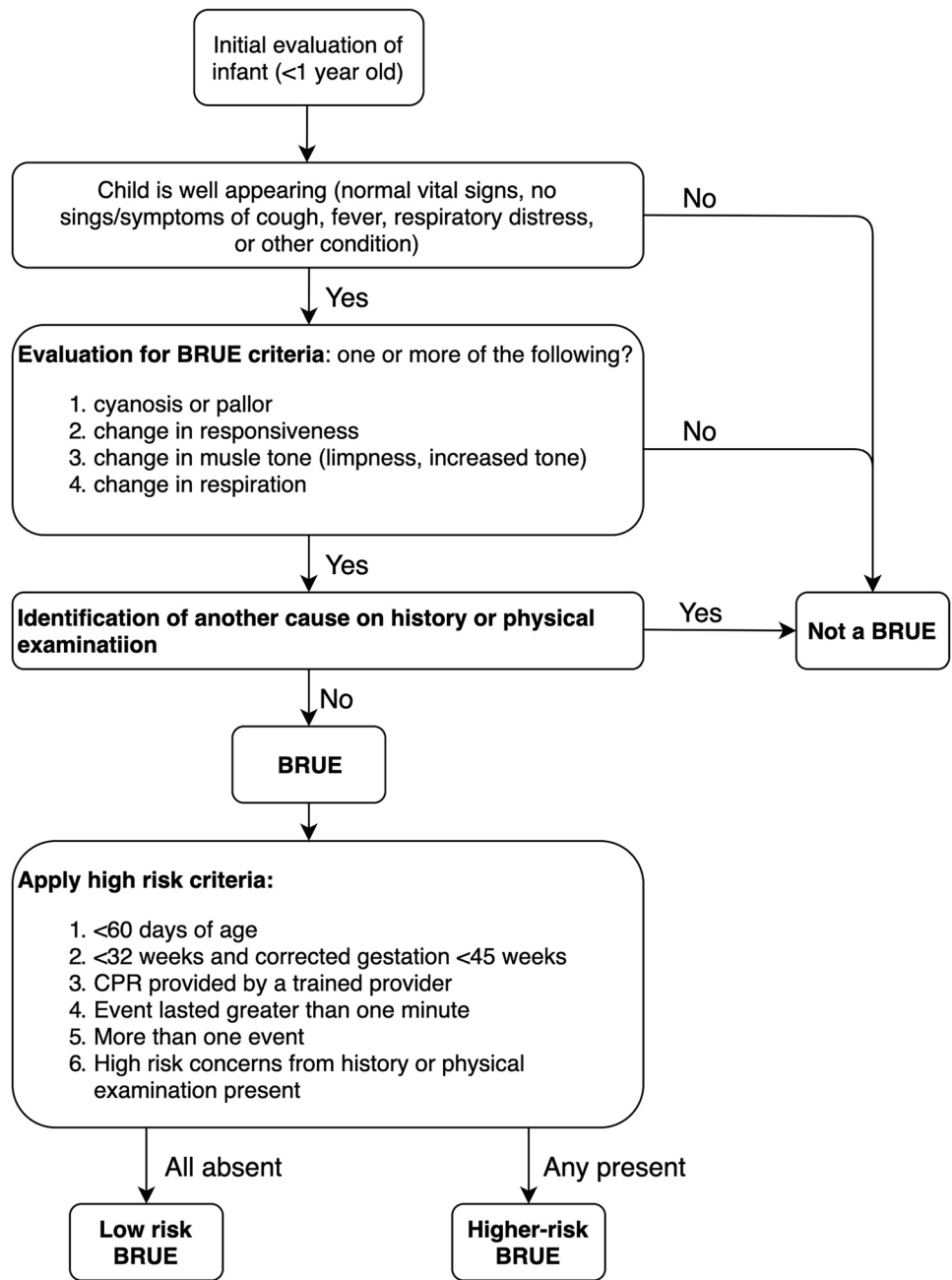
The AAP CPG provides recommendations for the management of lower-risk BRUE [1]. Most are provided as “moderate recommendations,” defined as those in which a particular action is favored because the anticipated benefits clearly exceed any potential harm and the quality of supportive evidence is good. A few recommendations, such as those with respect to admission, monitoring, electrocardiogram use, neuroimaging, and blood glucose measurement, are classified as “weak,” defined as those in which an action is favored because benefits clearly exceed harm, but for which supportive evidence is limited.

A summary of key recommendations from the CPG for lower-risk BRUE is provided in Fig. 2. Providers may briefly monitor patients with continuous pulse oximetry and serial observations. The CPG advocates against routine admission for observation alone. False positives may occur: brief periods of oxygen desaturation may be physiologic in young children, particularly during sleep [34]. The guideline suggests an observation period of 1–4 h, additionally stating pulse oximetry may have more value than cardiorespiratory monitoring alone.

Given the known risk of nonaccidental trauma among patients with BRUE [33], a thorough screening for social risk factors for child abuse is warranted. With respect to screening for infectious diseases, the CPG suggests obtaining a pertussis evaluation based on local disease prevalence and immunization practices and if testing can be performed with reasonable turnaround time. The guidelines suggest that an electrocardiogram may be beneficial. While the incidence of cardiac disorders as a cause for BRUE is unknown, the retrospective cohort study reported by Tieder et al. found two patients out of 2,036 included (<0.1%) had cardiac rhythm disorders, which were identified during outpatient subspecialty follow-up [33]. Similarly, prior research with ALTE has suggested that some patients without another explanation for the event have dysrhythmia or evidence of structural heart disease [35].

The CPG generally advocates against other tests or therapies [1]. With respect to cardiopulmonary evaluation, the CPG suggests that infants need not be admitted to the hospital for cardiorespiratory monitoring and advises against routine chest radiography, blood gas measurement, sleep

Fig. 1 Identification of brief resolved unexplained events (BRUE) and classification into lower- and higher-risk groups. CPR, cardiopulmonary resuscitation



studies, echocardiography, or initiation of home monitoring. The guidelines advocate against routine neuroimaging to evaluate for child abuse or neurologic disorders or the initiation of antiepileptic medication. With respect to infectious disease, the CPG advises against analysis of biomarkers from blood or CSF, cultures of blood, urine or CSF, chest radiography, and viral testing. The guideline advocates against testing for gastrointestinal disorders, including testing such as endoscopy or upper gastrointestinal series, and against initiation of acid suppression therapy. The CPG suggests avoiding testing for inborn errors of metabolism, including blood glucose, blood gas measurement, serum

lactic acid or bicarbonate, electrolytes, renal function testing, ammonia, urine organic acids, plasma amino acids, and plasma acylcarnitine. The CPG advocates against evaluation for potential anemia.

There is no evidence-based guideline for the management of higher-risk BRUE, as research evaluating events in these infants is limited. In 2019, the AAP published an expert consensus-derived framework for the management of these events [36]. Given the absence of robust evidence regarding higher-risk BRUE, these were constructed with the assistance of stakeholders from relevant subspecialties. Recommendations were provided in the

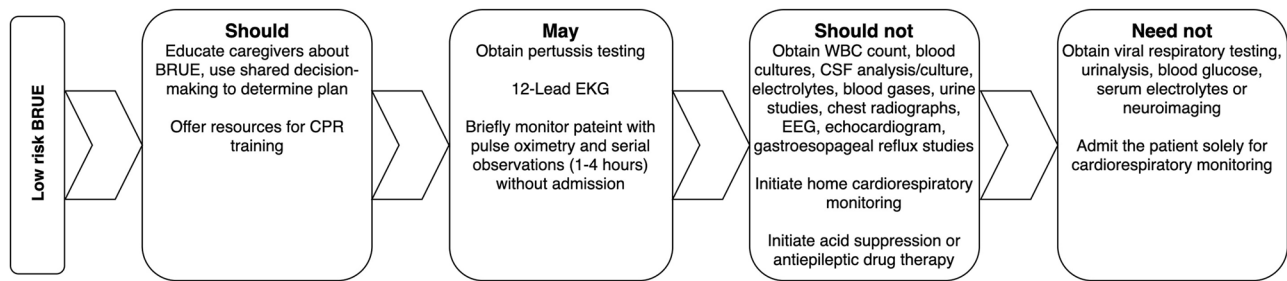


Fig. 2 Suggested management for lower-risk brief resolved unexplained events (BRUE), based on recommendations from the American Academy of Pediatrics' Clinical Practice Guideline. CPR, car-

diopulmonary resuscitation; EKG, electrocardiogram; WBC, white blood cell count; CSF, cerebrospinal fluid; EEG, electroencephalogram

context of potential etiology: child maltreatment, gastrointestinal, pulmonary (including obstructive and central sleep apnea and parenchymal disease), neurologic, cardiologic, infectious disease, and inborn errors of metabolism.

This guidance consists of an initial evaluation, preferably performed in the ED, continuous pulse oximetry, consultation with a social worker to screen for potential child abuse, and feeding evaluation (by a feeding therapist, if possible). Diagnostic evaluation can include electrocardiogram, a rapid viral respiratory panel, pertussis testing, hematocrit, and blood glucose testing. In children with concerns for child maltreatment, consultation with a child abuse expert is warranted, in addition to radiographic testing (skeletal survey and neuroimaging). Patients with additional concerns should be admitted to the hospital for a longer period of cardiorespiratory monitoring. Further steps should be taken based on the specific event. With suspected reflux, a gastroenterologist should be consulted. If sleep apnea is suspected, an otorhinolaryngologist and pulmonologist should be consulted, and a sleep study performed. If there is concern for central apnea, neuroimaging may be performed, in addition to consulting a pulmonologist. If there is concern for seizures, a prolonged (12 h) electroencephalogram may be considered, in addition to neurologist consultation. If there is concern for arrhythmia or structural heart disease, a cardiologist should be consulted. If an inborn error of metabolism is suspected, laboratory assessment should be performed, including assessment of glucose, electrolytes, blood urea nitrogen, calcium, and ammonia, and a geneticist should be consulted.

Future directions

The recent retrospective cohort study [33] provides baseline data on the association of BRUE with serious outcomes and suggests that the risk stratification guidelines may be an effective way at evaluating patients with BRUE. However,

more accurately identifying patients at BRUE who require specific types of investigations at the bedside remains a challenge and represents an important research need. Research is required to better characterize practice changes with BRUE, from the perspective of identifying unintended consequences and unnecessary variation in care. The changes suggested by the CPG have been projected to result in fewer hospitalizations of children with BRUE [37]. In one study of US children's hospital encounters, there was a decrease in the rate of admission of children with BRUE events following the CPG implementation (as much as 18% among patients > 60 days of age) [38]. Similar findings have also been reported in a single-center retrospective study [39]. Research is required to evaluate balancing effects, including serious outcomes that may be missed on their index visit. Another study reported that patients with BRUE continued to undergo low-yield diagnostic care (such as initiation of acid suppression therapy), suggesting the need for continued, institution-wide, quality improvement efforts [40]. One pilot study of a quality initiative, consisting of lecture based teaching, grand round lectures, posters, and individual feedback to providers in plan-do-study-act cycles every 3 months, supported the role of improvement efforts to decrease unnecessary admissions, neuroimaging, and chest radiography [41].

The findings that few patients with BRUE (< 5%) have serious conditions will likely be reassuring to caregivers [33]. From a qualitative aspect, future work is required to better involve parents in shared decision-making for BRUE. One study noted, for example, that parents of children admitted to the hospital for higher-risk BRUE felt reassured by hospitalization and diagnostic testing but remained unsettled about the lack of explanation for the child's event [42]. Another qualitative study conducted among 22 parents of children in the ED with BRUE suggested that parents' reactions to ED management of BRUE vary widely: greater than two-thirds expressed concern when asked about potential discharge from the ED rather than admission [43].

Conclusion

BRUE replaces ALTE and provides a definition with greater specificity which is now a diagnosis of exclusion. The use of this newer definition carries the benefit of allowing clinicians to identify alternative diagnoses, risk-stratify patients with BRUE, facilitate more rigorous research on outcomes, and improve quality improvement practices. While lower-risk BRUE occurs less frequently, there is evidence to support that such infants do not require routine hospitalization. For higher-risk BRUE, a cautious approach may be advisable, with potential admission, selective testing, and consultation as needed.

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Declarations

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