Supplemental Information

Additional information, rationale, and rare conditions.

RISK

It is important to understand higher-risk infants are not always at high risk for an adverse outcome. Neither the degree of risk for serious conditions nor the frequency of subsequent adverse events is known for higher-risk infants who experienced a BRUE. Finding the cause of the event or an underlying condition will allow more precise risk assessment and guide further management. The causes of these events remain heterogeneous, and most are not life-threatening. Serious adverse outcomes of events without a known cause or underlying condition are reported rarely.

The nonspecific nature of a BRUE, the dearth of relevant evidence, and the poor understanding of risk make the evaluation of higher-risk infants challenging. As in lower-risk infants, nonspecific and indiscriminate testing, such as broad use of complete blood cell counts and chest radiographs for all higher-risk infants, are unlikely to reveal an event's cause and may increase harm by leading to false-positives and further unnecessary testing.[3] We offer a tiered approach to consider in the evaluation and management of higher-risk infants after a BRUE.

HOSPITAL ADMISSION

For some higher-risk infants, a period of observation, either in the ED or an inpatient unit, may be helpful to observe for further events, await results of the initial workup, and facilitate consultations and/or evaluations, if indicated. Those centers where expert consultation is readily available and follow-up can be assured may choose to manage some infants as outpatients, whereas those with more limited availability may choose to admit or transfer to a medical center with a greater level of care. As telehealth services become more available, guidance from tertiary care pediatric subspecialists may be more accessible to local providers and remains a future area for research.

Hospital environments may put patients at risk for nosocomial infections and adverse patient safety events and can increase caregiver anxiety unnecessarily.

Untoward socioeconomic and family psychosocial dynamics have been associated with hospitalizing children with lower respiratory tract disease; similar dynamics may be reasonable to consider for higher-risk infants.[43]

SUBSPECIALTY EVALUATION

Child Maltreatment

Child maltreatment may have occurred even in well-appearing children and must be considered in the differential diagnosis of a higher-risk infant after a BRUE.

Children with AHT can present with a period of decreased responsiveness, seizures, trouble breathing, or apnea and, frequently, without any noticeable external trauma.[13] Researchers continue to seek effective biomarkers of AHT for screening.[44]

Of those missed AHT cases, 40.7% suffered medical complications, 27.8% were reinjured, and 2.8% died.[14]

Diagnosis of MCA requires a careful review of all available medical records. Some families in which maltreatment is occurring may present as ideal parents. Ethnicity, socioeconomic class, or family composition cannot be used to rule out maltreatment.

Certain risk factors increase the suspicion that child maltreatment might be occurring.[45] The caretaker should be observed for unusual anxiety, inability to accurately interpret the health status of the child, pressing for more and more unnecessary health care, and fabricated signs and symptoms when requesting health care.

Gastrointestinal

Relying on observed symptoms alone to diagnose GERD can be difficult in the first year of life, especially because symptoms do not always resolve with acid suppression therapy and the majority do not correlate with reflux episodes.[46–48] Thus, the major role of the evaluation of infants with GERD is to exclude other conditions that may mimic GERD, such as tracheoesophageal fistula, congenital dysphagia, esophageal stricture, or extraesophageal vascular slings.

Respiratory symptoms associated with feeding may be indistinguishable in a variety of conditions from nasopharyngeal reflux, cricopharyngeal achalasia, deep penetration, or microaspiration, so VFSS is needed to identify these problems that could not be diagnosed by a bedside feeding evaluation, which should serve as a first-tier test to identify respiratory symptoms associated with feeding in need of further diagnostic testing.

Clinicians can rarely consider MII-pH because there is only a weak correlation between reflux events detected during MII-pH studies and the presence of complications of reflux in this age group.[49] Esophagogastroduodenoscopy with biopsy may be considered in rare circumstances in the evaluation of infants in whom an underlying cause is not established by initial diagnostic testing and initial interventions. The subset of infants for whom esophagogastroduodenoscopy may be indicated are those with poor growth and feeding problems that do not improve with dietary changes, positioning, secondhand smoke avoidance, and feeding volume adjustments.[50,51]

The 2018 GERD practice guidelines suggest to consider to use pH-MII testing only to correlate persistent troublesome symptoms with acid and nonacid GER events or to clarify the role of acid and nonacid reflux in the etiology of esophagitis and other signs and symptoms suggestive of GERD.[52] Either of these indications may apply in the infant with suspected GERD and persistent respiratory events associated with feeding.

A UGI should not be used for the evaluation of GERD and is only indicated in the evaluation when anatomic abnormalities are suspected, such as tracheoesophageal fistula, vascular rings or slings, and esophageal strictures or webs or rings.[50] Additional studies, such as gastrointestinal scintigraphy or ultrasound, are not recommended in the routine evaluation of GERD in infants.[53]

Pulmonary

Oximetry is prone to motion artifact and therefore documented monitoring is recommended to confirm readings. Oximetry data must be interpreted in relation to age-appropriate normative data because brief, self-resolving oxygen desaturations and periodic breathing are often observed in otherwise well infants.[54,55]

In recurrent BRUE, testing for anemia by hemoglobin concentration should be initially considered in all higher-risk infants because anemia has been associated with multiple episodes of ALTE.[25] Also, a venous blood gas may be considered to measure carbon dioxide and bicarbonate levels to determine if an underlying respiratory or metabolic condition is present.

Although an arterial blood gas is the gold standard for evaluating the acid-base status and oxygenation, it is painful, technically challenging, and may cause injury and should be considered only rarely.

Only rare consideration should be given to chest radiographs or arterial blood gas without respiratory symptoms or constitutional illness, although they may be appropriate in young and premature infants.[31]

PSG consists of 8 to 12 hours of documented monitoring including EEG, electromyogram, oximetry, thoracic and abdominal excursion, airflow, and electrocardiogram, using standardized techniques.[56] PSG is considered to be the gold standard for identifying OSA, central sleep apnea, and periodic breathing and may identify seizures and other pathologies. Snoring may be absent in younger infants with OSA, including those with micrognathia, which may not be readily apparent on examination.[57]

Neurology

Examples of neurologic features of concern include family history (eg, the presence of an autosomal dominant pattern of benign infant seizures starting in the first weeks of life, suggesting a benign neonatal epilepsy syndrome), descriptions of the events (eg, abnormal eye movements suggesting opsoclonus), or observations of the parents (eg, weak handshake and mild facial diplegia, suggesting maternal myotonic dystrophy).

Neurocutaneous findings, such as the presence of ash-leaf spots or hypopigmented macules, may indicate tuberous sclerosis and concern for infantile spasms. Hypotonia and areflexia may suggest a neuromuscular disorder.

Routine EEG monitoring in low-risk ALTE patients has been shown to have low sensitivity and specificity for predicting subsequent development of epilepsy[11]; and even for patients with known epilepsy, a routine EEG has a sensitivity of only 58%.[58] However, a prolonged EEG (ie, 12+ hours) may have more use for detecting abnormalities.[59]

The use of brain MRI is unknown and thus would be considered rarely. Electromyogram, nerve conduction velocity testing, or genetic testing would not be considered in the acute setting.

Cardiology

In ~15% of patients with LQTS, the mutation is de novo[60] and thus not identifiable through family history. Also, even in untreated patients, only ~13% will have an aborted sudden cardiac death (SCD) or SCD episode.[61] If there are several family members with LQTS, the rate of SCD may be higher. A history of older adults with arrhythmias, such as atrial fibrillation in a grandfather, should not be

considered a positive family history in the evaluation of higher-risk infants.

After consultation with a pediatric cardiologist, rare consideration may include echocardiogram to consider cardiomyopathy (dilated or hypertrophic) and an anomalous left coronary artery from the pulmonary artery. An anomalous left coronary artery from the pulmonary artery requires a detailed echocardiogram, which can be used to identify the coronary artery origins and flow in diastole through these coronaries. Not all hospitals can be precise with this evaluation, and it is necessary to have a pediatric cardiologist reading the echocardiogram.

Infectious Disease

Basic information regarding family size, caretakers, and crowding may be helpful in assessing likelihood of exposure to infection. Respiratory infection should be considered in infants with a history of fever, cough, resolved cyanosis with coughing paroxysms, congestion, or rapid breathing or subtle findings of lethargy or marked irritability even without fever and/or physical findings of tachypnea, hypoxia, or increased work of breathing.

In recent data, it is suggested that apnea or an ALTE (based on literature before the definition of BRUE) at presentation of a respiratory viral infection may be associated with an array of other respiratory viruses.[62]

Increased risk for pertussis exposure is present in underimmunized families and communities, and the immunization history for the patient should be reviewed. If further history suggests increased risk for pertussis exposure or additional episodes of gagging, gasping, or color change with respiratory pause occur during the period of observation, pertussis testing should be considered, along with empiric antibiotic therapy if results are not promptly available.

Subtle findings of coryza may not be apparent on initial physical examination, but if seen during an observation period, additional tests for respiratory viruses and/or pertussis should be considered.

IEMs

Elevations of lactic acid >2 mmol/L were found in 54% of 65 infants after an ALTE but in only 15% in those whose levels were >3 mmol/L. Of those with >3 mmol/L, 5 of 7 had a "specific, serious diagnosis" (the specific diagnoses were not named).[31] Decreased serum bicarbonate levels <20 mmol/L have been found in up to 20% of reported ALTE cases, but these were associated with sepsis or seizures, not IEMs.[31] Abnormal bicarbonate results were found in 9 of 215 cases, with only 3 being significant, again, with no clarifying diagnosis present.[3] Blood glucose levels also may be considered in higher-risk infants diagnosed with a BRUE.

Of note, although bedside glucose may have been performed in the initial presentation because it is a common prehospital and ED test, measurement of serum glucose in ALTE was mentioned in only 3 reports and none included their findings.[3,31,63]

Although electrolytes (sodium, potassium, chloride, blood urea nitrogen, creatinine) are often measured, these are reported as abnormal in only 0% to 4.3%.[3,31,63] Serum calcium has been reported rarely and is abnormal in 0% to 1.5% of patients, although 20% of patients with a clinical suspicion of vitamin D deficiency were found to have hypocalcemia.[64]

Elevated ammonia levels did not lead to a confirmed IEM in 2 reports[31,33] but may have been a factor in another report on recurrent ALTE.[36] Measurement of blood gas did not contribute to the final diagnosis in 2 reports.[31,33] This may reflect the fact that these potential disorders (eg, urea cycle disorders and organic acidemias) would not be likely to self-resolve and so, therefore, would not meet the definition of a BRUE.

Only rarely should urine organic acids and plasma amino acid testing be done for the higher-risk infant after a BRUE because these have shown a low positive rate after an ALTE.[31] Abnormalities of plasma acylcarnitines have not been reported after an ALTE, although this is the diagnostic test for fatty acid oxidation disorders and so could be rarely considered in the higher-risk infant, especially in the context of hypoglycemia.

Appropriate genetic evaluation should include obtaining an appropriate medical and family health history, selection of genetic testing laboratories, selection of the genetic testing, review and approval of payer coverage for the testing, discussion of potential genetic testing results, and confirmation of follow-up of these results with discussion of implications of results with management and treatment.

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