

Review of the Brief Resolved Unexplained Events 2.0 (BRUE 2.0) Criteria for Infants

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Abstract

Most (96%) patients presenting with brief resolved unexplained events (BRUE, formerly apparent life-threatening event or ALTE) do not have a serious underlying diagnosis*. The AAP guidelines do not help differentiate infants with such diagnoses from those without. The BRUE 2.0 tool is designed to determine which infants presenting with BRUE are at low risk for having a serious underlying diagnosis as well as those who are at risk for recurrent events.

II. HOW TO USE

When to Use

This tool is designed to be used in infants presenting after an acute episode of change (decrease) in alertness, responsiveness, respiratory effort, skin color (eg cyanosis), or muscle tone. The tool should be applied only to infants in whom the episode has resolved and who do not have an alternative explanation for the event. For example if the event was a choking spell caused by gastroesophageal reflux, it would not qualify as a “BRUE.”

Pearls / Pitfalls

Infants must be asymptomatic at the time of evaluation with a physical exam that does not suggest an alternative diagnosis. Underlying medical conditions do not preclude the use of this calculator, but one should consider whether those conditions could have caused the event (eg seizure disorder, cardiac disease).

BRUE remains a nebulous diagnosis, even in the age of refined clinical prediction rules and society (AAP) guidelines as evidenced by the rule’s very low specificity (8.6%) and AUROC (0.64 in the derivation model). In an external validation study a revised model yielded an AUROC for “serious underlying diagnosis” of 0.71. The sensitivity of the rule is high (95.3% in the derivation study & 100% in the validation study) for prediction of a serious underlying diagnosis, meaning that the absence of all “high risk factors” can be useful for “ruling out,” an underlying diagnosis, but the presence of any high risk factor is far less predictive of whether an underlying diagnosis may be present. This limitation stems from the de-

cision tool’s use of a composite outcome of the presence of one among a long list of serious underlying diagnoses.

This decision rule is therefore best used in aiding a discussion of risks, benefits, and shared decision-making with families regarding the utility (or lack thereof) in diagnostic testing or hospitalization.

Why to Use

This decision tool provides a percentage risk of a “serious underlying diagnosis” and for the likelihood that a similar event will reoccur. The American Academy of Pediatrics promotes shared decision-making with the patient’s caregivers regarding the decision to admit for observation versus discharging home for close follow-up. This decision should take into account the caregivers’ values and comfort level with uncertainty of diagnosis.

III. NEXT STEPS

Advice

Many families will appreciate a more concrete percentage risk of recurrence and of a serious underlying condition, which this decision tool provides. The AAP provides written instructions and advice regarding the diagnosis of a BRUE on their [website](#). The key is to engage in a discussion of shared decision-making with caregivers regarding the risks and benefits of discharge home versus admission versus observation in the ED. Many providers will recommend admission for all babies presenting with a BRUE if they are under 60 days old, although this is not a strict rule or a universal practice.

Additional helpful interventions for patients being discharged home is the provision of CPR training. Caregivers should also be able to follow up with their pediatrician within a short time frame, as well as be able to present for re-evaluation if the event recurs.

Management

Testing and treatment should be tailored toward the presenting history and physical exam, with consideration for an underlying infectious process, evaluation for seizure disorders, or child abuse, as indicated by the clinical context. Respiratory viral testing and testing for *Bordetella pertussis* or *parapertussis* can be considered for high risk patients (known exposure, unvaccinated status, etc.)

Clinical social workers, if available, can assist in screening for caregivers' resource needs and risk factors for child abuse and/or neglect.

If reflux or aspiration are being considered, evaluation by a speech pathologist or other qualified professional can aid in securing safer feeding methods for the patient.

Critical Actions

Remember to consider child abuse in patients presenting with a BRUE or BRUE-like episode.

Ill-appearing infants, particularly those less than 60 days of age, should be evaluated for sepsis, even in the absence of fever or hypothermia.

IV. EVIDENCE

Evidence Appraisal

Nama et al. (2022) derived a clinical decision tool from a cohort of 3283 eligible patients designed to estimate risk of a serious underlying condition as well as the risk of event recurrence. The AAP guidelines (released in 2016) provide recommendations for the work-up and management of infants presenting with BRUEs, but they tended to overly classify patients as higher risk for having a serious underlying condition.

Of the 3283 included infants, 150 had a serious underlying diagnosis. The main risk factors associated with a serious underlying diagnosis were: history of a similar event (OR 1.86, 95% confidence interval [CI] 1.34-2.57), history of event clusters (OR 1.66, 95% CI 1.19-2.30), the need for CPR (OR 2.38, 95% CI 1.09-5.53), and an abnormal medical history (OR 1.92 95% CI 1.09-5.53). Their results differed somewhat from the AAP guidelines' recommendations in that infants older than 60 days of age were actually *more* likely to have a serious diagnosis.

A total of 469 of the cohort's patients had a recurrent event. Having 1 or more high risk AAP criteria present was associated with a higher odds of recurrence (OR 5.00, 95% CI 2.80-9.00). Prematurity (gestational age <

32 weeks or corrected age <45 weeks with gestational age 32-38 weeks) (OR 1.53, 95%CI 1.22-1.92), history of a similar event (OR 2.34, 95% CI 1.92-2.86), event clusters (OR 3.70, 95% CI 3.02-4.53), and abnormal medical history (OR 1.58, 95% CI 1.29-1.93) were associated with higher odds of recurrence as well. Recurrence was more common (OR 1.40, 95% CI 1.14-1.71) in infants ≤ 60 days of age.

The main strength of this derivation study lies in its goal of predicting patient-centered outcomes. Specifically, the clinical decision tool can help the patient's care team discuss how high or low the risk of serious causes requiring intervention as well as that of event recurrence with patients' families. The AAP promotes shared decision-making as an important part of the management of and determination of disposition for these patients, and this tool can help guide that discussion.

The performance of this tool is relatively modest; its area under the receiver operating curve (AUROC) for predicting a serious underlying diagnosis was 0.64 (95% confidence interval 0.59–0.70) in the training data set and 0.61 (95% CI 0.49–0.72) in the validation data set. This is numerically higher but not statistically significantly different than AUROCs obtained using the AAP guidelines' criteria. Furthermore it is important to note that many of the outcomes' 95% confidence intervals are quite wide, indicating low precision in the results.

This study is limited by its relatively small (150) number of patients with the primary outcome of interest as well as that it was biased toward younger infants and full-term infants. It should be used with caution in preterm infants especially.

A follow-up external validation study in 2024 (Nama et al. in JAMA Pediatrics) included a cohort of 1042 infants. Similar to the derivation cohort, most infants were aged 60 days or younger. The BRUE prediction rule had an AUROC of 0.60 (95% CI 0.54-0.67) for detecting a serious underlying condition in this cohort, similar to the derivation cohort. A revised model had an AUROC of 0.71 (95% CI 0.65-0.76). This represents an improvement compared to the AUC for the AAP high risk criteria (0.53 for both serious underlying condition and event recurrence).

The validation study has similar limitations to the derivation paper, specifically in that the primary outcome of interest was relatively low frequency (79/1042) and in that the sample was biased toward younger infants. The other demographic characteristics were similar between the two studies, with both being derived from North American cohorts (USA for the derivation study and Canada for the validation study). With such a low prevalence of the outcomes of interest, the predictive values are therefore quite limited. The "serious underlying conditions" used in developing the BRUE guidelines (and these prediction models) are nebulous and are mainly

useful for conveying a general idea of risk as opposed to being able to narrow down a differential diagnosis.

Overall, as a screening test, the BRUE decision tool performs well, with very high sensitivity (95.3%) and negative predictive value (97.5%). However it has very low specificity, which increases the frequency of false positive results. Additionally, different clinicians may have different comfort levels in terms of what a “high risk” of a significant underlying condition might be. Finally, these criteria and prediction tools are based on retrospective data, which may limit their ultimate clinical utility.

Full list of “serious underlying conditions” (Supplemental Table 4):

- Seizure or epilepsy
- Airway abnormality
- Dysphagia or GERD
- Respiratory infection
- Apnea
- Bacterial infection
- Child abuse
- Other CNS abnormalities
- Surgical GI abnormality
- Electrolyte abnormalities
- Cardiac arrhythmia
- Other (pulmonary regurgitation, accidental ingestion, foreign body, near suffocation, death (no identified diagnosis), cystic fibrosis)

Formula

To be classified as BRUE, all of the following must be true:

- Infant <1 year old.
- Asymptomatic on presentation (no URI symptoms, no fever).
- No explanation for the event after conducting history and physical (e.g. GER, feeding difficulties).
- History of sudden, brief, and now resolved episode consisting of ≥ 1 of the following:
 - Cyanosis or pallor.
 - Absent, decreased, or irregular breathing.
 - Marked change in tone (hyper or hypotonia).
 - Altered level of responsiveness.

The risk of serious underlying condition and the risk of recurrent event are calculated based on the following inputs:

- Age, days.
- History of similar event.*
- History of multiple events or event clusters.*
- Abnormal medical history.*
- Prematurity (<32 weeks or between 32-38 weeks and corrected to <45 weeks).*
- Absent, decreased, or irregular breathing.*
- Marked change in tone (hyper or hypotonia).*

*Yes = 1, No = 0

% risk of serious underlying condition = $[e^x / (1 + e^x)] * 100$,

where $x = -2.9 - 0.0046 * (\text{Age, days}) + 1.22 * (\text{History of similar event}) + 0.35 * (\text{Abnormal medical history})$

% risk of recurrent event = $[e^w / (1 + e^w)] * 100$,

where $w = -2.82 + 0.65 * (\text{History of similar event}) + 0.98 * (\text{History of multiple events or event clusters}) + 0.28 * (\text{Prematurity}) + 0.36 * (\text{Cyanosis or pallor}) + 0.16 * (\text{Absent, decreased, or irregular breathing}) + 0.23 * (\text{Marked change in tone})$

Facts & Figures

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- Other (pulmonary regurgitation, accidental ingestion, foreign body, near suffocation, death (no identified diagnosis), cystic fibrosis)

Literature

Original/Primary

<https://pubmed.ncbi.nlm.nih.gov/35965279/>

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Validation

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