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ORIGINAL ARTICLE

Diagnostic testing for evaluation of brief resolved unexplained events

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Abstract

Background: Since the publication of the American Academy of Pediatrics (AAP) clinical practice guideline for brief resolved unexplained events (BRUEs), a few small, single-center studies have suggested low yield of diagnostic testing in infants presenting with such an event. We conducted this large retrospective multicenter study to determine the role of diagnostic testing in leading to a confirmatory diagnosis in BRUE patients.

Methods: Secondary analysis from a large multicenter cohort derived from 15 hospitals participating in the BRUE Quality Improvement and Research Collaborative. The study subjects were infants < 1 year of age presenting with a BRUE to the emergency departments (EDs) of these hospitals between October 1, 2015, and September 30, 2018. Potential BRUE cases were identified using a validated algorithm that relies on administrative data. Chart review was conducted to confirm study inclusion/exclusion, AAP risk criteria, final diagnosis, and contribution of test results. Findings were

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stratified by ED or hospital discharge and AAP risk criteria. For each patient, we identified whether any diagnostic test contributed to the final diagnosis. We distinguished true (contributory) results from false-positive results.

Results: Of 2036 patients meeting study criteria, 63.2% were hospitalized, 87.1% qualified as AAP higher risk, and 45.3% received an explanatory diagnosis. Overall, a laboratory test, imaging, or an ancillary test supported the final diagnosis in 3.2% (65/2036, 95% confidence interval [CI] 2.7%–4.4%) of patients. Out of 5163 diagnostic tests overall, 1.1% (33/2897, 95% CI 0.8%–1.5%) laboratory tests and 1.5% (33/2266, 95% CI 1.0%–1.9%) of imaging and ancillary studies contributed to a diagnosis. Although 861 electrocardiograms were performed, no new cardiac diagnoses were identified during the index visit.

Conclusions: Diagnostic testing to explain BRUE including for those with AAP higher risk criteria is low yield and rarely contributes to an explanation. Future research is needed to evaluate the role of testing in more specific, at-risk populations.

INTRODUCTION

Well-appearing infants commonly present for medical attention after a brief event characterized by abrupt change in color (cyanosis or pallor), breathing (central or obstructive apnea), muscle tone (hyper- or hypotonicity), and/or level of alertness. In 2016, the American Academy of Pediatrics (AAP) published a clinical practice guideline (CPG) that updated the term from apparent life-threatening event (ALTE) to brief resolved unexplained event (BRUE).[1] This guideline includes a more precise definition for these events and recommends limited diagnostic testing and subspecialty consultation for patients categorized as lower risk.[1] At the time of the guideline there was insufficient evidence for the AAP to provide recommendations for higher risk BRUE patients, which new studies suggest make up most of the patients presenting to emergency departments (EDs).[2] A subsequent publication outlines a consensus-based framework for testing in higher risk patients based on clinical presentation, but the authors note a paucity of objective evidence to support their recommendations.[3]

Brand et al.[4] reported that only 5.9% of tests were contributory in patients presenting with an ALTE. The low yield of testing in ALTE was confirmed by a number of other studies as well.[5,6] Testing in patients with BRUE has decreased nationally since publication of the CPG and small studies have demonstrated limited yield of testing.[7–9] A better understanding of the yield of diagnostic testing is needed to guide management for patients being evaluated for a BRUE. Nonspecific low-yield testing, particularly in populations where there is low prevalence of disease can lead to false-positive or ambiguous results and unnecessary hospitalization, procedures, and radiation exposure and additional uncertainty. The primary aim of this retrospective multicenter hospital study was to determine how often diagnostic testing contributes to an explanatory diagnosis in patients evaluated for lower and higher risk BRUE.

METHODS

Administrative data from 15 U.S. hospitals wee used to identify infants < 1 year of age with discharge diagnostic International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes related to BRUE. All study patients were discharged between October 1, 2015, and September 30, 2018. Our study period starts when the ICD-10 code (R68.13) was introduced. This includes a 7-month period prior to publication of the AAP BRUE guideline.[1] The Pediatric Health Information System (PHIS) database was queried for 11 of the hospitals that participate in PHIS. Four hospitals that did not participate in PHIS used an identical ICD-10 search strategy. We applied four ICD-10 coding strategies to identify potential study subjects while minimizing sampling bias. Although this approach involves the review of many patients who by medical record review will not qualify for study participation, it reduces underclassification of rare causes or overclassification from BRUE ICD-10 code use. First, to identify all possible codes used for BRUE patients, we rank ordered the discharge diagnoses used in conjunction with patients assigned the ALTE/BRUE ICD-10 code (R6813). We then classified these codes and the ALTE/BRUE ICD-10 code into four discrete coding groups or "cohorts." Cohort 1 included patients with a primary or secondary ICD-10 discharge code of ALTE/BRUE (R6813). Cohort 2 included patients with discharge codes indicating common BRUE symptoms such as "apnea" or "color change." We included Cohorts 3 and 4 to identify patients presenting with a BRUE but that did not receive the ALTE/BRUE code because the event was eventually explained by a specific diagnosis. Cohort 3 included serious conditions such as child abuse and airway abnormalities while cohort 4 included less serious diagnoses such as gastroesophageal reflux (GER) or viral infections.[2] Patients with codes for extreme prematurity (because they are likely to have many comorbidities excluding them from the BRUE definition and

would therefore not warrant a full chart review) and transfers from outside hospitals (potential lack of all relevant presenting information) were excluded (P07.01, P07.02, P07.21–P07.25.). The details of this strategy including ICD codes are listed in our group's prior publications.[2,10] Medical record review was used to confirm AAP BRUE and lower risk versus higher risk criteria. Patients were excluded by chart review if they presented with symptoms/signs that were not consistent with the AAP definition of a BRUE (for example, abnormal vital signs, cough, respiratory distress, fever), if they did not have at least one BRUE characteristic, if they had abnormalities on initial examination, or if they had a preexisting condition that could explain the BRUE, such as known seizure disorder. Lower risk was defined per the AAP CPGs as an event with age at the time > 60 days, gestation > 32 weeks, and postconception age > 45 weeks; no cardiopulmonary resuscitation (CPR) performed by medical provider; first event; no repeat events; and no major concerns on history or physical examination (e.g., history of neglect or evidence of unexplained bruising). For all infants included in the database, including the older ones likely to not have prematurity coded, gestational age was assessed by manual data review. The administrative data were validated and supplemented for each subject by having local trained investigators perform medical record review at all sites to (1) confirm eligibility; (2) determine risk factors and event characteristics; (3) determine final diagnoses; and (4) determine any laboratory or ancillary testing, if any results were abnormal, and if the abnormal results contributed to the final diagnosis. We distinguished results that were true positive (contributory) versus false positive (noncontributory). Each chart reviewer trained until an interrater reliability of 0.80 was achieved. Discharge documentation was used to determine final discharge diagnoses.

Outcome measures

The primary outcome of interest is whether a laboratory test or study contributed to an explanation for the BRUE. Secondarily we determined the rate of false-positive results. Testing was only included in the analysis if done during the index visit.

Laboratory testing

Laboratory tests were considered abnormal if the results were outside the age-specific ranges based on published norms.[11] An abnormal test was considered contributory to the BRUE explanation if the documentation from the provider's final discharge assessment was based on the laboratory abnormality. If labs were abnormal but did not contribute to a particular diagnosis, they were considered false positive. Blood, urine, and cerebral spinal fluid (CSF) cultures were considered positive and contributory if the patient received a full course of antimicrobials targeting an identified pathogen.

Diagnostic imaging and ancillary tests

Imaging and ancillary tests were considered contributory if the report noted an abnormality that supported a diagnosis explaining the BRUE. Findings that did not explain the event with biologic plausibility were considered noncontributory (e.g., head CT to evaluate for subdural bleeds with an incidental finding of choroid plexus cyst).

Statistical analysis

Patient demographic characteristics were summarized and compared by whether or not testing was performed. Diagnostic testing was compared by ED disposition and AAP risk stratification. The latter was compared using chi-square tests for categorical variables. The proportion of contributory diagnostic testing was determined by dividing the number of contributory results by the total number of tests performed. The rate of false positivity was calculated as false-positive (FP) results divided by the sum of FP and true-negative (TN) results (FP rate = FP/(FP+TN)). We calculated various test characteristics including true-positive rate, false-positive rate, and positive predictive value (PPV) for all the tests. All statistical analyses were performed using SAS v.9.4 (SAS Institute) and a $p < 0.05$ was considered statistically significant. This study was approved by the institutional review board from each of the participating hospitals. Data were managed using a REDCap (Research Electronic Data Capture) database maintained by the Institute of Translational Health Sciences.[12]

RESULTS

Of the 5584 patients who underwent medical record review, 2036 (36.5%) met BRUE inclusion criteria. Of these, 1286 (63.2%) were hospitalized, 1774 (87.1%) met AAP higher risk criteria, and 45.3% received an explanation for their event by the end of the ED or inpatient stay (Table 1). Of these patients, 1430 (70.2%) had at least one test performed. Higher risk patients were more likely to have laboratory tests or imaging done when compared to the lower risk group (71.9% vs. 58.4%, $p < 0.001$). The proportion of lower risk patients with any laboratory testing was 27.5% (72/262) and imaging 55.3% (145/262). The corresponding numbers for higher risk patients were 47% (834/1774) and 64% (1141/1774, $p < 0.001$). Based on disposition, 14.8% (111/750) of patients discharged home from the ED had laboratory testing and 35.9% (269/750) imaging. The corresponding proportions for hospitalized patients were 62% (795/1286) for labs and 79% (1017/1286) for imaging ($p < 0.001$).

The most frequently obtained laboratory tests were complete blood count (CBC; 28.8%), electrolytes (29.5%), liver function tests (LFTs; 14.2%), urinalysis (11.1%), and viral respiratory testing (15.0%). Electrocardiogram (ECG; 42.3%), chest radiograph

TABLE 1 Patient demographics.

	Overall	No testing	Testing	*p*-value
N	2036	606 (29.8)	1430 (70.2)	
Age (days)	46 (18–103)	53 (20–118)	43.5 (18–100)	0.005
Male gender	971 (47.7)	279 (46)	692 (48.4)	0.331
Hospitalized	1286 (63.2)	158 (26.1)	1128 (78.9)	<0.001
Race/ethnicity				
Non-Hispanic White	740 (36.3)	205 (33.8)	535 (37.4)	0.002
Non-Hispanic Black	659 (32.4)	224 (37)	435 (30.4)	
Hispanic	446 (21.9)	110 (18.2)	336 (23.5)	
Other	191 (9.4)	67 (11.1)	124 (8.7)	
Insurance				
Government	1306 (64.1)	395 (65.2)	911 (63.7)	0.773
Commercial	685 (33.6)	197 (32.5)	488 (34.1)	
Other	45 (2.2)	14 (2.3)	31 (2.2)	
Received an explanation for event	923 (45.3)	297 (49)	626 (43.8)	0.030
Meet AAP lower risk criteria	262 (12.9)	109 (18)	153 (10.7)	
Meet AAP higher risk criteria	1774 (87.1)	497 (82)	1277 (89.3)	<0.001
LOS (days)	1 (1–2)	1 (1–1)	1 (1–2)	<0.001

Note: Data are reported as median (IQR) or *n* (%).

Abbreviations: AAP, American Academy of Pediatrics; LOS, length of stay.

TABLE 2 Frequency of laboratory testing for patients who present with BRUE.

	Overall	Discharged from ED	Hospitalized[a]	AAP lower risk	AAP higher risk	*p*-value
Total	2897	215	2682	168	2729	
CBC	587 (28.8)	48 (6.4)	539 (41.9)	36 (13.7)	551 (31.1)	<0.001
Electrolytes	601 (29.5)	51 (6.8)	550 (42.8)	41 (15.6)	560 (31.6)	<0.001
LFTs	289 (14.2)	24 (3.2)	265 (20.6)	19 (7.3)	270 (15.2)	0.001
Urinalysis	226 (11.1)	13 (1.7)	213 (16.6)	13 (5)	213 (12)	0.001
Urine culture	180 (8.8)	10 (1.3)	170 (13.2)	11 (4.2)	169 (9.5)	0.005
Blood culture	184 (9)	9 (1.2)	175 (13.6)	7 (2.7)	177 (10)	<0.001
CRP	85 (4.2)	2 (0.3)	83 (6.5)	1 (0.4)	84 (4.7)	0.001
CSF culture	77 (3.8)	1 (0.1)	76 (5.9)	1 (0.4)	76 (4.3)	0.002
Pertussis	50 (2.5)	3 (0.4)	47 (3.7)	5 (1.9)	45 (2.5)	0.540
Viral respiratory test	305 (15)	22 (2.9)	283 (22)	14 (5.3)	291 (16.4)	<0.001
Blood gas	152 (7.5)	18 (2.4)	134 (10.4)	9 (3.4)	143 (8.1)	0.008
Metabolic labs[b]	161 (14.4)	14 (0.4)	147 (5.8)	11 (4.1)	150 (8.4)	0.014
Total patients with one or more laboratory test	901 (44.3)	109 (14.5)	792 (61.6)	72 (27.5)	829 (46.7)	<0.001

Abbreviations: AAP, American Academy of Pediatrics; BRUE, brief resolved unexplained event; CBC, complete blood count; CRP, C-reactive protein; CSF, cerebrospinal fluid; LFT, liver function test.

[a]All tests were performed more commonly among hospitalized patients, $p < 0.001$.

[b]These include plasma lactic acid, ammonia, amino acids, acyl carnitine, and urine organic acids.

(CXR; 33.5%), and electroencephalogram (EEG; 11.1%) were the most common diagnostic tests. Pertussis testing was performed in 2.5% of higher risk patients versus 1.9% of lower risk patients ($p < 0.001$). ECGs were obtained in a similar proportion of higher risk versus lower risk patients (42.6% vs. 40.5%, $p = 0.52$; Tables 2 and 3).

TABLE 3 Frequency of imaging/ancillary testing for patients who present with BRUE.

	Overall	Discharged from ED	Hospitalized[a]	AAP lower risk	AAP higher risk	*p*-value
Total	2266	357	1909	215	2051	
ECG	861 (42.3)	196 (26.1)	665 (51.7)	106 (40.5)	755 (42.6)	0.520
Chest radiograph	683 (33.5)	131 (17.5)	552 (42.9)	60 (22.9)	623 (35.1)	<0.001
Echocardiogram	165 (8.1)	9 (1.2)	156 (12.1)	11 (4.2)	154 (8.7)	0.013
EEG	226 (11.1)	4 (0.5)	222 (17.3)	19 (7.3)	207 (11.7)	0.034
Head ultrasound	111 (5.5)	2 (0.3)	109 (8.5)	7 (2.7)	104 (5.9)	0.034
Brain CT	78 (3.8)	13 (1.7)	65 (5.1)	8 (3.1)	70 (3.9)	0.482
Brain MRI	59 (2.9)	2 (0.3)	57 (4.4)	2 (0.8)	57 (3.2)	0.027
pH probe	31 (1.5)	0 (0.0)	31 (2.4)	1 (0.4)	30 (1.7)	0.106
UGI	30 (1.5)	0 (0.0)	30 (2.3)	1 (0.4)	29 (1.6)	0.116
Video fluoroscopic swallow study	22 (1.1)	0 (0.0)	22 (1.7)	0 (0.0)	22 (1.2)	0.070
Total patients with one or more study	1284 (63.1)	269 (35.9)	1015 (78.9)	145 (55.3)	1139 (64.2)	0.006

Abbreviations: BRUE, brief resolved unexplained event; EEG, electroencephalogram; UGI, upper gastrointestinal.

[a]All tests were performed more commonly among hospitalized patients, $p < 0.001$.

Laboratory tests contributed to a diagnosis in 1.1% of tests obtained (33/2897, 95% CI 0.8%–1.5%). These included three cases of electrolyte disturbances, one abdominal trauma with elevated LFTs, four urinary tract infections, one case of bacteremia, two patients with pertussis, and 19 patients with bronchiolitis/viral respiratory tract infections. In the single case of bacteremia, the blood culture grew a typical contaminant species (*Staphylococcus hominis*) but the patient was treated with a full course of antibiotics (Table 4).

Imaging and ancillary studies contributed to an explanatory diagnosis in 1.5% of such studies performed (33/2266, 95% CI 1.0%–1.9%). These included 2/683 (0.3%) chest radiographs showing pneumonia and 8/226 (3.5%) EEGs consistent with seizure disorder. Of the neuroimaging studies, 3/248 (1.2%) were abnormal and consistent with two diagnoses of stroke and one case of abusive head trauma. Severe GER was diagnosed in 10/31 pH probe studies. Similarly, 1/30 upper gastrointestinal (UGI) studies and 5/22 video fluoroscopic swallow studies confirmed oropharyngeal aspiration (OPA). Although 861 ECGs were performed, no new cardiac diagnoses were identified during the index visit (Tables 4 and 5).

Overall, a laboratory test, imaging, or other ancillary testing supported the final diagnosis in 3.2% (65/2036, 95% CI 2.7%–4.4%) of patients. These included 19 cases with a viral respiratory disease based on identification of a virus in a nasopharyngeal sample and 10 with GER identified on pH probe study. For many frequently ordered laboratory tests such as CBC, electrolytes, LFTs, and blood gases, the false-positive rate was high, ranging from 20.2% to 69.1%, and PPV was low (Tables 4 and 5). For tests that have definitive binary results that do not require interpretation such as blood, urine, and CSF cultures, the false-positive rate was low, ranging from 1.2% to 3.6%. For diagnostic testing, 164 (19%) of ECGs and 198 (29%) CXRs had false-positive or incidental findings.

DISCUSSION

In this large multicenter retrospective cohort study, we demonstrate that diagnostic testing in patients with BRUE remains common but is low yield, even in patients designated as higher risk by the AAP CPG. Out of over 5000 diagnostic tests, only 1.3% contributed to a final diagnosis. Although 70.2% of all subjects had some testing, in only 3.2% of patients was the final diagnosis supported by those tests. Most notably, testing with ECG as recommended by the AAP did not lead to the detection of any cardiac arrhythmias or congenital heart disease as originally intended. More testing discrimination for patients presenting with a BRUE could greatly improve the quality of care for these patients and their families.[7,13]

Viral respiratory pathogen identification was the test with the most positives (19), but it is unclear how often the diagnosis alters management since there is no specific treatment. There could be value in testing in an infant who presents with an apneic episode and later develops cough, shortness of breath, or recurrent apneic events during hospitalization. Similarly, pH probes and UGI studies were often used by clinicians to make a diagnosis of GER but evidence-based guidelines do not recommend this testing because of their high false-positive rate and temporal disassociation between abnormal finding and the BRUE.[14] Video fluoroscopic swallow studies contributed to a diagnosis of OPA in 23% of subjects in our study compared to a 72% rate in the single-center study by Duncan et al.[9]

In accordance with the BRUE CPG, higher risk patients were more likely to have laboratory test or imaging done when compared to the lower risk group (72% vs. 58.4%). However, considering that more than half of all lower risk patients had some testing, there is scope of improvement in this group as well.

Many labs and ancillary studies had high rates of false positivity and therefore low specificity and PPV. Routine screening for serious

TABLE 4 Diagnostic yield of laboratory testing.

Labs	Total	Total positive	Total negative	TP	FP	TN	FPR (95% CI)	% TP (95% CI)	PPV (95% CI)	Diagnoses associated with test results
Overall	2897	726	2171	33	693	2171	24.2 (22.6 to 25.8)	1.1 (0.8 to 1.5)	4.5 (3 to 6.1)	
CBC	587	119	468	0	119	468	20.3 (17 to 23.5)	0 (0 to 0)	0 (0 to 0)	
Electrolytes	601	228	373	3	225	373	37.6 (33.7 to 41.5)	0.5 (−0.1 to 1.1)	1.3 (−0.2 to 2.8)	Hyponatremia, hypocalcemia, hypoglycemia
LFTs	289	108	181	1	107	181	37.2 (31.6 to 42.7)	0.3 (−0.3 to 1)	0.9 (−0.9 to 2.7)	Abdominal trauma
Urinalysis	226	30	196	3	27	196	12.1 (7.8 to 16.4)	1.3 (−0.2 to 2.8)	10 (−0.7 to 20.7)	Urinary tract infection
Urine culture	180	10	170	4	6	170	3.4 (0.7 to 6.1)	2.2 (0.1 to 4.4)	40 (9.6 to 70.4)	Urinary tract infection
Blood culture	184	4	180	1	3	180	1.6 (−0.2 to 3.5)	0.5 (−0.5 to 1.6)	25 (−17.4 to 67.4)	Bacteremia
CRP	85	16	69	0	16	69	18.8 (10.5 to 27.1)	0	0	
CSF culture	77	1	76	0	1	76	1.3 (−1.2 to 3.8)	0	0	
Pertussis	50	2	48	2	0	48	0	4 (−1.4 to 9.4)	100	Pertussis
Viral respiratory test	305	48	257	19	29	257	10.1 (6.6 to 13.6)	6.2 (3.5 to 8.9)	39.6 (25.7 to 53.4)	Bronchiolitis or VRTI
Blood gas	152	105	47	0	105	47	69.1 (61.7 to 76.4)	0	0	
Metabolic labs[a]	161	55	106	0	55	106	34.2 (26.8 to 41.5)	0	0	

Note: FN value for all tests was considered zero.

Abbreviations: CBC, complete blood count; CRP, C-reactive protein; CSF, cerebrospinal fluid; FN, false negative; FP, false positive; FPR, false-positive ratio; LFT, liver function test; PPV, positive predictive value; TN, true negative; TP, true positive (contributary); VRTI, viral respiratory tract infection.

[a]These include plasma ammonia, amino acids, acyl carnitine, and urine organic acids.

TABLE 5 Diagnostic yield of imaging/ancillary testing.

Imaging	Total	Total positive	Total negative	TP	FP	TN	FPR	% TP	PPV	Diagnoses associated with test results
Overall	2266	596	1670	33	559	1670	25.1 (23.3 to 26.9)	1.5 (1 to 1.9)	5.5 (3.7 to 7.4)	
ECG	861	164	697	0	164	697	19 (16.4 to 21.7)	0 (0 to 0)	0 (0 to 0)	
Chest radiograph	683	198	485	2	196	485	28.8 (25.4 to 32.2)	0.3 (−0.1 to 0.7)	1 (−0.4 to 2.4)	Pneumonia
Echocardiogram	165	75	90	0	75	90	45.5 (37.9 to 53.1)	0	0	
EEG	226	25	201	8	17	201	7.8 (4.2 to 11.4)	3.5 (1.1 to 5.9)	32 (13.7 to 50.3)	Seizure (including infantile spasms)
Head ultrasound	111	26	85	0	26	85	23.4 (15.5 to 31.3)	0	0	
Brain CT	78	11	67	1	10	67	13 (5.5 to 20.5)	1.3 (−1.2 to 3.8)	9.1 (−7.9 to 26.1)	Abusive head trauma
Brain MRI	59	21	38	2	19	38	33.3 (21.1 to 45.6)	3.4 (−1.2 to 8)	9.5 (−3 to 22.1)	Ischemic/hemorrhagic stroke
pH probe	31	15	16	10	5	16	23.8 (5.6 to 42)	32.3 (15.8 to 48.7)	66.7 (42.8 to 90.5)	GERD
UGI	30	13	17	1	12	17	41.4 (23.5 to 59.3)	3.3 (−3.1 to 9.8)	7.7 (−6.8 to 22.2)	OPA
Video fluoroscopic swallow study	22	8	14	5	3	14	17.6 (−0.5 to 35.8)	22.7 (5.2 to 40.2)	62.5 (29 to 96)	OPA
Other imaging	142	30	112	4	26	112	18.8 (12.3 to 25.4)	2.8 (0.1 to 5.5)	13.3 (1.2 to 25.5)	
CT face			0	1		0				Choanal atresia
Sleep study			0	1		0				Apnea of prematurity
Laryngoscopy			0	2		0				Airway abnormality

Note: FN value for all tests was considered zero.

Abbreviations: FN, false negative; FP, false positive; FPR, false-positive ratio; GERD, gastroesophageal reflux disease; OPA, oropharyngeal aspiration; PPV, positive predictive value; TN, true negative; TP, true positive (contributary); UGI, upper gastrointestinal.

diagnoses such as seizure and abusive head trauma is unlikely to be cost-effective and would lead to unnecessary workup in many patients. However, this workup should not be withheld where there are concerning historical features as is illustrated in our study population where brain imaging was performed in 137 (6.7% of imaging/ancillary tests) and EEG in 226 subjects (11.1% of imaging/ancillary tests) with true-positive rates of 2.2% and 3.5%, respectively. The current AAP BRUE CPGs suggest that providers "may" consider pertussis testing and screening ECGs. In this study, we show that considering the low incidence of pertussis, providers appropriately are not routinely testing for it. In contrast, ECG is the most ordered diagnostic test in both lower and higher risk patients, which suggests adherence to the CPGs, but with extremely low yield. In our study, ECG did not identify any cardiac diagnoses during the index hospital visit thus showing low utility when used as a screening tool in this population. Our finding of low yield of diagnostic testing in infants presenting with a BRUE-like event is in agreement with other similar single-center studies on the topic and with that of ALTE literature.[4–9] Considering that BRUE is defined in a narrower way excluding any patient with abnormal vital signs or examination, it stands to reason that testing will have low yield whether in lower or higher risk infants with BRUE.

The results from our study may be helpful to providers in the ED and on the inpatient floors when making shared decisions with families about the benefits of diagnostic testing for unexplained events. Providers and families often fear that the event could be a symptom of a serious underlying condition, but several studies have found low rates of serious diagnoses in patients who present with BRUE.[2] A recent meta-analysis found no increased risk of death over baseline risk in the first year of life after a BRUE.[15] Providers may offer diagnostic tests and this may be necessary in some scenarios to provide reassurance, but the impact of false-positive results should also be considered. As an example, ECGs are often ordered to rule out cardiac arrythmias but in our cohort there were no new cardiac diagnoses and false-positive ECGs often led to cardiology consults, ECGs, and additional hospital monitoring.

LIMITATIONS

Our study is limited by its retrospective nature. The wide spectrum of final diagnoses assigned to patients who present with a BRUE-like event makes it difficult to accurately identify the population of interest.[15–17] It is possible that our search strategy or sample size made us underpowered to detect some serious diagnoses, such as metabolic disorders or congenital heart disease. We also may have missed some serious diagnoses in patients who never underwent testing or returned to medical attention at a hospital outside of the research collaborative. In addition, our study period starts when the ICD-10 code (R68.13) was introduced. This includes a 7-month period prior to publication of the AAP BRUE guideline. A number of factors minimize the possibility and effect of misclassification of ALTE versus BRUE patients before, during, and after the publication of the BRUE CPG. Our approach casts a wide net and then only includes those patients that qualify based on medical record review. This study was nested within both a quality improvement and research collaborative that had multiple aims and included the validation of our approach to identify these patients.[10] This knowledge of our approach reassures us that the included patients would have qualified as a BRUE under the 2016 inclusion criteria. The ICD-9/10 code for ALTE and BRUE is the same (R68.13), so changes in coding were not a substantial issue. The administrative data were validated and supplemented for each subject by having local trained investigators perform medical record review at all sites. This does limit our ability to assess adherence to BRUE CPGs. Finally, with this study design we could not assess the added reassurance or stress that evaluation provides to health care providers and families.

CONCLUSIONS

This large multicenter study shows that while diagnostic testing is commonly performed for brief resolved unexplained event presentations, it rarely contributes to identifying serious diagnoses, whether in lower or higher risk patients. Screening tests should be considered only when the clinical assessment suggests a diagnosis other than brief resolved unexplained event. In addition, our data indicate that the American Academy of Pediatrics recommendation to consider electrocardiogram testing should be reconsidered.

AUTHOR CONTRIBUTIONS

Manoj K. Mittal, Joel S. Tieder, and Allayne Stephans conceptualized and designed this study, designed the data collection tools, collected data, performed the analysis, drafted the initial manuscript, and reviewed and revised the manuscript. Kathryn Westphal, Risa Bochner, Adam Cohen, Jennifer Y. Colgan, Atima C. Delaney, Amy M. DeLaroche, Thomas Graf, Beth Harper, Ron L. Kaplan, Hannah C. Neubauer, Mark I. Neuman, Nirav Shastri, and Victoria Wilkins conceptualized and designed the study, designed the data collection tools, collected data, and reviewed and revised the manuscript. Erin Sullivan and Matt Hall conceptualized the study, coordinated the supervised data collection, managed data including data quality, reviewed the manuscript, and performed data analysis. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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