In Press

The Management and Outcome of Brief resolved unexplained event (BRUE) in Pediatric Intensive Care Unit: A Single Tertiary Center Experience

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Abstract

Objectives:

We aim to describe the current practice and management for patients presented with Brief Resolved Unexplained Event (BRUE) & their outcome over three years at the tertiary pediatric intensive care unit. We also looked for the proportion of inappropriate use of BRUE as admission diagnosis and the ratio of low-risk and high-risk BRUE patients in our PICU.

Methods:

A retrospective cohort study conducted at King Fahad Medical City between 2017 and 2020 that included all infants from 28 days up to one year of age who were admitted with the diagnosis of BRUE to the pediatric intensive care unit (PICU) at King Fahad Medical City (650 admissions per year) over 3 years. All infants with a diagnosis of cyanotic heart disease, infants who are on home oxygen, and infants more than 1 year of age were excluded. The diagnosis of BRUE was defined based on the American Academy of Pediatrics (AAP) BRUE guidelines published in 2016.

Results:

Over 3 years period, we collected a total of 48 infants. 37 infants were male and 11 females. There was a statistically significant association between BRUE and with history of prematurity or other medical problems. 68.7% of the admission to the PICU did not fit the BRUE diagnosis of AAP 2016. Only 15 infants (31.3%) fit the diagnosis of AAP 2016 of BRUE, with 7 infants out of the 15 (46.7%) fit as low-risk BRUE while 8 infants (53.3%) were fit as high-risk BRUE.

Conclusion:

Following the AAP guidelines is necessary to avoid over diagnosis of BRUE, especially in the low-risk group that can be managed outside PICU.

Keywords: AAP; American Academy of Pediatrics, ALTE; apparent life-threatening event, BRUE; Brief Resolved Unexplained Event, HFNC; high flow nasal cannula, PICU; pediatric intensive care unit.

Introduction:

BRUE is defined based on specific criteria including events occurring in infants younger than one year. It has a transient nature and lacks clear cause whenever the observer reports a sudden, brief, and now resolved episode of ≥1 of the following: (1) cyanosis or pallor; (2) absent, decreased, or irregular breathing; (3) marked change in tone (hyper- or hypotonia); and (4) altered level of responsiveness. (1) BRUE is usually lasts <1 minute but typically <20–30 seconds, and then the patient return to the baseline state of health. [(1)] In the American Academy of Pediatrics (AAP) 2016 replaced the term the apparent life-threatening event (ALTE) with the brief resolved unexplained event (BRUE). [(1)] Patients presenting with BRUE usually have reassuring history, physical examination, and vital signs at the time of clinical evaluation. AAP also classified BRUE into low-risk and high-risk BRUE. [(1)]

Infants with Low-risk BRUE have all of the following: (1) the age more than 60 days, gestational age equal to or more than 32 weeks, and post-conceptional age is more than 45 weeks, (3) first event with no recurrence, (4) duration of the event is less than 1 minute, (5) no concerning features in history or physical examination and (6) did not have cardiopulmonary resuscitation (CPR) by a trained medical provider. [(1)] AAP has published clinical practice guidelines for the low-risk group to minimize unnecessary admission and workup. [(1)] In a meta-analysis published in 2018, the reported mortality risk for infants with low-risk BRUE was comparable to the mortality risk of otherwise healthy infants in the first year of life. [(2)] In another single-center retrospective study, infants with low-risk BRUE had a good prognosis in the long-term follow-up. [(3)]

It is often challenging for clinicians to decide on an infant with low-risk BRUE or reassure caregivers and discharge him home, particularly if they have unreliable historians or caregivers. On the other hand, unnecessary admission of low-risk BRUE and extensive workup impact the health care system, wasting medical resources and increasing bed utilization. Proper Identification of low-risk BRUE upon presentation and following AAP guidelines in its management is crucial and may prevent wastage of resources without adding risk to the child. AAP management guidelines of low-risk BRUE were validated and proved to be safe, and cost-effective to the health care system, leading to fewer hospital admissions among infants and diagnostic testing. [(4-7)] The hospital admission rate, diagnostic testing, and length of stay decreased over time after implementing the published AAP Low-risk BRUE guidelines and recommendations. [(7)] Sriram

Ramgopal did one study that found that applying AAP criteria for BRUE on Patients previously diagnosed with ALTE succeeded in identifying those with high-risk criteria and high mortality and morbidity. [8]

In our center, we lack clear diagnostic criteria and management guidelines for cases presented with BRUE. We hypothesize that admissions to the hospital with BRUE are over-diagnosed and admitted with unnecessary excessive workup & consultations of other specialties. We also hypothesize that low-risk BRUE admissions to the pediatric intensive care unit (PICU) are frequent and often unnecessary. We aim to describe the current practice of BRUE management & outcome in our hospital over the past three years. We also aim to obtain the proportion of low-risk and high-risk BRUE and the proportion of unnecessary admissions and workups.

Methods:

Study design and population: We conducted a retrospective cohort study that included all infants below one year of age who were admitted with the diagnosis of BRUE to the pediatric intensive care unit (PICU) at King Fahad Medical City (650 admissions per year) over 3 years, from January 2017 to March 2020. We excluded infants with a diagnosis of cyanotic heart disease, infants who are on home oxygen, and infants more than 1 year of age.

Data collection: We searched the database and reviewed all charts that were labeled with admission diagnoses of ALTE, BRUE, cyanosis, apnea, and/or change in tone. We collected data from chart review on patients' characteristics, demographic data, the clinical presentation documented by the admitting physician, and detailed event history, including the presenting symptoms, the event duration, recurrence), and the past medical history and if cardiopulmonary resuscitation was performed or not. Furthermore, we collected data on the patient's management in the PICU, need for oxygen or respiratory support, consultations requested, workup requested, and if any was abnormal, length of hospital /PICU stays. We also looked at the hospital outcome and the discharge diagnosis.

The research team rechecked all patients' diagnosed upon admission based on the data collected and compared it to the BRUE definition by the American Academy of Pediatrics (AAP) in BRUE guidelines published in 2016. [1] For this study's purpose, we classified the patients if it is fitting BRUE or ALTE or none of them and if it fits High-risk or low-risk BRUE.

Statistical analysis:

All categorical variables, including gender and gestational age, were presented as proportions. Continuous variables, such as age at admission and duration of invasive ventilation, were expressed as medians (interquartile range [IQR]). Parametric tests were used to compare groups for normally distributed variables and non-parametric tests were used when data were skewed. Chi-square and Fisher's exact test used to compare categorical variables, with the latter being used when the cell expected frequency was smaller than 5. A p-value less than 0.05 was considered statistically significant. All data were entered and analyzed through the statistical package SPSS 25 (SPSS Inc., Chicago, IL, USA).

Results

Patients characteristics:

A total of 48 patients were included in the study, 37 were males (77.1%), and 11 were females (22.9%). 68.7% of the admission to the PICU did not fit the BRUE diagnosis of AAP 2016. Only 15 infants (31.3%)

fit the diagnosis of AAP 2016 of BRUE, with 7 patients out of the 15 (46.7%) fit as low-risk BRUE while 8 patients (53.3%) were fit as high-risk BRUE. Patients who did not fit BRUE either fit the definition of ALTE 29 (60.4%) or did not fit either 4 (8.3%).

The majority of patients were less than 2 months old, 28 (58.3%), while 19 patients were 2-6 months (39.6%) and 1 (2.1%) more than 6 months. 17 patients (35.4%) were premature. 29 patients (60.4%) had associated comorbidity, including CHD, CLD, BPD, GIT disease, underlying neurological condition, or others.

13 of the admitted patients (7.1%) required a simple oxygen supply for hypoxia, 10 patients (20.8%) required HFNC for a median duration of 3 days, while 14 of them (29.2%) required non-invasive ventilation for a median duration of 2 days, and 10 of them (20.8%) required invasive ventilation for a median duration of 9 days. The median PICU length of stay was 3 days.

Furthermore, 38 patients (79.2%) required more than 3 workups frequently echocardiography, electroencephalography (EEG), and brain images. Also, 17 patients (35.4%) required more than 3 consultations for other specialties.

There was a statistically significant association between BRUE in infants with other health problems and prematurity. The P-value = 0.01 and 0.031 respectively.

Nasopharyngeal aspiration ((NPA) for virology was a frequent test in infants admitted with BRUE. NPA results were positive in 22 patients. Only 3 of them (21.4%) were fit BRUE. NPA resulted negative in 21 patients with 11 of them (78.6%) being fit BRUE.

Discussion:

Our retrospective cohort study describes the current practice, management, and outcome of infants admitted with a diagnosis of BRUE based on clinical suspicion rather than following the AAP guidelines. Over 3 years period, we collected a total of 48 infants who were admitted to PICU with the diagnosis of BRUE or ALTE.

The majority of patients (37) were admitted through the emergency department, with predominant male infants, a total of 37. The median age is 2 months with 35.4% of them having a history of prematurity and 60.4% of our patients had an associated other health condition. Our center is considered a tertiary care center that serves a diversity of complex pediatric cases.

All patients were below 6 months of age except one patient that was above 6 months. This could be explained by the fact that younger infants are at higher risk of developing BRUE and getting admitted to the hospital. A high proportion of patients, 79.2%, had 3 or more workups in addition to subspecialty consultations which confirms the high demand and resources utilization.

After applying the AAP 2016 definition of BRUE, We found that only a third of the patients fit the BRUE diagnosis between low-risk and high-risk groups. In our study, the median PICU length of stay was 3 days while the overall median of hospital length of stay was 6.5 days. Our results showed a higher length of stay in comparison to a previous study that showed 0.32- 2.31 days. [(9)], Among patients who required respiratory support, 10 patients (20.8%) required invasive mechanical ventilation, and 4 of them fit BRUE. No

difference between the high-risk BRUE group and the low-risk group in invasive ventilatory support, 2 from each group were required for a median duration of 9 ventilatory days.

Also, there was no major difference between low-risk and high-risk BRUE infants in terms of performing >3 workups upon admission to PICU (6 low-risk infants and 7 high-risk infants) but the high-risk group had more than 3 consultations performed for 3 patients in the high-risk group and one in the low-risk infant with statistically insignificant; P-Value 0.31.

The outcome of our patients who fit the BRUE definition (15 patients), 13 infants were discharged home, 1 infant was transferred to other hospitals, and 1 died due to septic shock.

4 patients were diagnosed after completing their workup upon discharge home, 1 case reached diagnosis on the follow-up, while the rest 9 cases continued their follow-up without a clear diagnosis.

Conclusion:

Following the AAP guidelines is necessary to avoid over-diagnoses of BRUE and unnecessary workups and consultations, especially for the low-risk group.

We encourage all tertiary PICDs to implement the AAP BRUE guidelines to fairly allocate the medical resources.

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Characteristics	Description	n(n%)
Gender	Male	37 (77.1)
	Female	11 (22.9)
Age upon admission (Months)	<2	28 (58.3)
	2 – 6	19 (39.6)
	> 6	1 (2.1)
Prematurity <37	Yes	17 (35.4)
	No	31 (64.6)
Corrected age 45 weeks or less at presentation	Yes	21 (43.8)
	No	27 (56.3)
Admitted through	ER	37 (77.1)
	Ward	8 (16.7)
	Other	3 (6.3)
Past medical History	Healthy	19 (39.6)
	Unhealthy	29 (60.4)
CHD		9 (18.8)
CLD , BPD		6 (12.5)
GIT		5 (10.4)
Neurology disease		10 (20.8)
Others		20 (41.7)
Fit BRUE		**15 (31.3)**
Low Risk BRUE		**7 (16.3)**
High RISK BRUE		**8 (16.7)**
Not BRUE- Fit ALTE		29 (60.4)
Not BRUE-Not ALTE		4 (8.3)

Table -1: Clinical characteristics of patients (n = 48)

Abbreviations: CHD; congenital heart disease, CLD; chronic lung disease, BPD; bronchopulmonary dysplasia, GIT; gastrointestinal malformation.

Management & Outcome	Description	n(n%)
O_2 ONLY	Yes	13 (27.1)
HFNC	Yes	**10 (20.8)**
	No	38 (79.2)
NIV (CPAP-BiPAP)	Yes	**14 (29.2)**
	No	34 (70.8)
Invasive MV (intubated)	Yes	10 (20.8)
	No	38 (79.2)
Blood gas result	Normal	26 (59.1)
	Abnormal	18 (40.9)
Any culture performed	Done	43 (89.6)
Any Positive Culture	Positive	9 (20.5)

	Negative	35 (79.5)
Type of positive culture	Blood	2 (22.2)
	Urine	5 (55.6)
	Other	2 (22.2)
NPA	Done	43 (89.6)
NPA result	Positive	**22 (51.2)**
	Negative	21 (48.8)
Workup 3 or less	Yes	10 (20.8)
Workup more than 3	Yes	**38 (79.2)**
Consultation to other specilities 3 or less	Yes	31 (64.6)
Consultation to other specilities more than 3	Yes	17 (35.4)
Final Diagnosis upon discharge	Yes	**23 (47.9)**
	No	25 (52.1)
Patient's Outcome	Death	1 (2.1)
	Discharge home	**45 (93.8)**
	Transferred to Other Facility	2 (4.2)
Reached Diagnosis after discharge in the last follow up	Yes	7 (28.0)
	No	**18 (72.0)**

Table 2- Patient management

Abbreviations: NIV; non invasive ventilation, CPAP, BiPAP, NPA

Table – 3: Descriptive analysis of continuous variables

Variables	**Minimum**	**Maximum**	**Median (IQR)**
Age upon admission (Months)	0.20	15.00	2(3 - 1.05)
HFNC days	1	3	3 (3 – 1)
NIV days	1.00	6.00	2(2.25 - 1)
Invasive Ventilation days	1	92	9(14 - 4)
Number of workup	0	10	5(6 - 4)
Number of consultation	0	7	3(4 - 2)
Length of PICU stay (days)	1	92	3(5 - 2)
Length of hospital stay (days)	3	120	6.5(16.75 - 5)

Table – 4: Effect and association of BRUE and non-BRUE cases with study characteristics

Characteristics	**Description**	**Fit BRUE**		***P - value***
		Yes (n = 15)	**No (n = 33) (%)**	
Gender	Male	12 (80.0)	25 (75.8)	0.746
	Female	3 (20.0)	8 (24.2)	
Age upon admission (Months)	<2	10 (66.7)	18 (54.5)	0.628
	2 - 6	5 (33.3)	14 (42.4)	
	> 6	0 (0.0)	1 (3.0)	
Prematurity <37	Yes	2 (13.3)	15 (45.5)	*0.031
	No	13 (86.7)	18 (54.5)	
	Yes	4 (26.7)	17 (51.5)	0.100

Corrected age 45 weeks or less at presentation	No	11 (73.3)	16 (48.5)	
Past medical History	Healthy	10 (66.7)	9 (27.3)	*0.010
	Have co-morbidity	5 (33.3)	24 (72.7)	
O_2 ONLY	Yes	4 (26.7%)	9 (27.3%)	0.965
	No	11 (73.3%)	24 (72.7%)	
HFNC	Yes	2 (13.3%)	8 (24.2%)	0.388
	No	13 (86.7%)	25 (75.8%)	
NIV (CPAP-BiPAP)	Yes	4 (26.7%)	10 (30.3%)	0.797
	No	11 (73.3%)	23 (69.7%)	
Invasive MV (intubated)	Yes	4 (26.7%)	6 (18.2%)	0.502
	No	11 (73.3%)	27 (81.8%)	
Type of positive culture	Blood	0 (0.0%)	2 (28.6%)	0.358
	Urine	2 (100.0%)	3 (42.9%)	
	Other	0 (0.0%)	2 (28.6%)	
NPA	Done	14 (93.3%)	29 (87.9%)	0.566
	Not done	1 (6.7%)	4 (12.1%)	
NPA result	Positive	3 (21.4%)	19 (65.5%)	*0.007
	Negative	11 (78.6%)	10 (34.5%)	
Workup <= 3	Yes	2 (13.3%)	8 (24.2%)	0.388
	No	13 (86.7%)	25 (75.8%)	
Workup > 3	Yes	13 (86.7%)	25 (75.8%)	0.388
	No	2 (13.3%)	8 (24.2%)	
	No	9 (90.0%)	9 (60.0%)	

Table – 5: Association of subgroup analysis of high and low risk BRUE with study characteristics

Characteristics	**Description**	**Low and High Risk BRUE**		***P - value***
		Low (n = 7)	**High (n = 8)**	
Gender	Male	6 (85.7%)	6 (75.0%)	0.605
	Female	1 (14.3%)	2 (25.0%)	
Age upon admission (Months)	<2	5 (71.4%)	5 (62.5%)	0.714
	2 - 6	2 (28.6%)	3 (37.5%)	
Prematurity <37	Yes	1 (14.3%)	1 (12.5%)	0.919
	No	6 (85.7%)	7 (87.5%)	
Corrected age 45 weeks or less at presentation	Yes	1 (14.3%)	3 (37.5%)	0.310
	No	6 (85.7%)	5 (62.5%)	
Admitted through	ER	4 (57.1%)	6 (75.0%)	0.512
	Ward	2 (28.6%)	2 (25.0%)	
	Other	1 (14.3%)	0 (0.0%)	
Past medical History	Healthy	4 (57.1%)	6 (75.0%)	0.464
	Unhealthy	3 (42.9%)	2 (25.0%)	
CHD	Yes	2 (28.6%)	1 (12.5%)	0.438
	No	5 (71.4%)	7 (87.5%)	
CLD , BPD	Yes	0 (0.0%)	1 (12.5%)	0.333
	No	7 (100.0%)	7 (87.5%)	

GIT	Yes	1 (14.3%)	0 (0.0%)	0.268
	No	6 (85.7%)	8 (100.0%)	
Neurology disease	Yes	2 (28.6%)	1 (12.5%)	0.438
	No	5 (71.4%)	7 (87.5%)	
Others	Yes	2 (28.6%)	1 (12.5%)	0.438
	No	5 (71.4%)	7 (87.5%)	
Blood gas result	Normal	4 (57.1%)	4 (57.1%)	0.999
	Abnormal	3 (42.9%)	3 (42.9%)	
Any Positive Culture	Positive	1 (14.3%)	1 (12.5%)	0.919
	Negative	6 (85.7%)	7 (87.5%)	
NPA	Done	7 (100.0%)	7 (87.5%)	0.333
	Not done	0 (0.0%)	1 (12.5%)	
NPA result	Positive	3 (42.9%)	0 (0.0%)	0.051
	Negative	4 (57.1%)	7 (100.0%)	
Workup <= 3	Yes	1 (14.3%)	1 (12.5%)	0.919
	No	6 (85.7%)	7 (87.5%)	
Workup > 3	Yes	6 (85.7%)	7 (87.5%)	0.919
	No	1 (14.3%)	1 (12.5%)	
Consultation to other services 3 or less	Yes	6 (85.7%)	5 (62.5%)	0.310
	No	1 (14.3%)	3 (37.5%)	
Consultation to other services more than 3	Yes	1 (14.3%)	3 (37.5%)	0.310
	No	6 (85.7%)	5 (62.5%)	
Final Diagnosis Reached upon discharge ?	Yes	2 (28.6%)	2 (25.0%)	0.876
	No	5 (71.4%)	6 (75.0%)	
Outcome	Death	1 (14.3%)	0 (0.0%)	0.267
	Discharge home	5 (71.4%)	8 (100.0%)	
	Transferred to Other Facility	1 (14.3%)	0 (0.0%)	
Diagnosis in patient chart in last f/u reached ?	Yes	1 (25.0%)	0 (0.0%)	0.197
	No	3 (75.0%)	6 (100.0%)	