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Editorial

Gastro-oesophageal reflux is not a major cause of brief resolved unexplained events in infants

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Introduction

The clinical scenario of an infant presenting to the emergency department with the parents reporting a history of the child stopping breathing, choking or “turning blue” at home is a well-recognised event and accounts for between 2.5 and 4.1 hospital admissions per 1000 live births [1, 2]. The infant is often back to their normal self with a normal clinical examination. This event used to be called an apparent life-threatening event (ALTE) [1] and recently it has been suggested that it should now be called a brief resolved unexplained event (BRUE) [2]. Gastro-oesophageal reflux (GOR) has long been considered to be a common reason for an ALTE and some studies have listed it as an underlying cause in up to 54% of patients [3–6]. Does the evidence support this belief?

ALTEs and BRUEs

The term ALTE was proposed in 1986 [1] and, prior to this, such events were classified as “near-miss sudden infant death syndrome (SIDS)” [6]. It became clear that babies with near-miss events were not at increased risk of SIDS, and this terminology was replaced with the term ALTE [1, 6]. It was considered that this new term was both vague and subjective. Symptoms appearing frightening to caregivers, such as periodic breathing, could be manifestations of normal neonatal physiology [7]. In 2016, the American Academy of Pediatrics (AAP) released a

clinical guideline for practitioners recommending that the term ALTE be replaced by BRUE [2]. The aim was to allay the anxiety to the caregivers brought about by the use of the term ALTE, as well as to give practitioners clear management guidance by stratifying such infants into high- and low-risk groups.

It should be clear that a BRUE is diagnosed only when there is no other explanation for a qualifying event, following an appropriate history and thorough physical examination. The AAP guidelines give clear guidance for the management of low-risk infants and these infants can be managed safely at home. A recent meta-analysis of the risk of death in infants who have experienced a BRUE supports the return-home management approach. The risk of death is about the same as the baseline risk of death during the first year of life. For patients evaluated in an emergency department and deemed as low risk, there is no need for them to be investigated and admitted to hospital [8]. The AAP guideline does not provide recommendations for investigation of those that are stratified in the high-risk group.

GOR and gastro-oesophageal reflux disease

National Institute for Health and Care Excellence (NICE) guidelines published in 2015 are very clear about the definitions of GOR and gastro-oesophageal reflux disease (GORD). GOR is “The passage of gastric contents into the oesophagus. It is a common



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Although it is often stated that gastro-oesophageal reflux is the most common cause of a brief resolved unexplained event or apparent life-threatening event, there are very few data to support the hypothesis of cause and effect <http://bit.ly/2FjknUy>



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physiological event that can happen at all ages from infancy to old age and is often asymptomatic. It is more common after feeds or meals. In many infants it is associated with a tendency to “overt regurgitation” – the visible regurgitation of feeds” [9]. GORD is “Gastro-oesophageal reflux that causes symptoms (for example, discomfort or pain) severe enough to merit medical treatment or that has associated complications (such as oesophagitis or pulmonary aspiration)” [9].

GOR is very common in infants for several reasons, including the physiological low tone of the lower oesophageal sphincter in infancy, liquid feeds and supine position, and occurs in about 40% of infants. Onset is usually before 8 weeks of age and may be frequent, with 5% of those affected having six or more episodes a day. It does not usually need further investigation or treatment [9]. NICE, in 2015, commented that GOR causes episodes of apnoea or ALTEs only rarely, but physicians should consider referral for specialist investigations if reflux is suspected as a possible factor [9]. The Pediatric Gastroesophageal Reflux Clinical Practice Guidelines from 2018 list BRUEs as one of the 23 signs and symptoms of GORD but do not make a comment about the likely prevalence of this presenting symptom [10]. One of the biggest difficulties about examining the effect of GOR on BRUEs is that there is a huge variation in definitions, investigative tools, outcome measures and prevalence reports used in the literature on GOR [11, 12]. For example, pH studies, regarded by many as the standard diagnostic tool for GOR, only measures acid reflux (pH <4). It is difficult to interpret studies in infants with a presumed association between apnoea and GOR based on pH studies because the buffering effect of feeding may result in predominantly non-acid GOR. Patients potentially at risk cannot be reliably identified by pH studies. Exclusive use of pH is therefore not suitable for the detection of all GOR-associated apnoeas in infants. The pH-independent multichannel intraluminal impedance (MII) technique is a more sensitive diagnostic tool for this approach [13].

Methods

A search of the literature was performed using the following PECO (population, exposure, control, outcome) question: “In previously well infants (population), are those with GOR (exposure) compared to infants with no GOR (control) more likely to present with a BRUE (outcome)?”

To find primary sources, Medline was searched *via* PubMed and Embase was searched separately, using the following terms: “GE Reflux” OR “Gastroesophageal Reflux” AND “BRUE” OR “Brief Resolved Unexplained Event” OR “ALTE” OR “Apparent life-threatening episode” OR “Apnoea”. The Cochrane library was searched in January 2019 with the terms “GE Reflux” AND “BRUE” OR “ALTE” OR “Apnoea”.

Results

The search strategy resulted in 153 citations, and after removing some duplicates and non-English-language studies, abstracts of 117 papers were reviewed. The hospital librarian (Abdul Sulaiman, Sidra Medical Library, Doha, Qatar) assisted with the literature search and retrieval of some original articles. The majority of articles were review articles or retrospective case note reviews of cases admitted with the diagnosis of ALTE to see what causative aetiology was considered. No relevant reviews were identified. A total of 12 articles were deemed relevant to our clinical question. All articles were separately reviewed by N.Z. Jilani and A. Hussain, and included one systematic review (including eight studies) [3], two retrospective note reviews [14, 15] and nine prospective investigative studies [13, 16–23] (table 1).

Discussion

There continues to be much debate about the underlying aetiology of BRUEs and whether GOR is causative [6, 24]. MEYER *et al.* [25] retrospectively reviewed infants admitted with the diagnosis of ALTE. Re-applying the BRUE definition to this group, they found only 23% of subjects falling within the definition of BRUE and only one of the 87 patients in their review fitted the low-risk BRUE criteria. This illustrates the difficulty in the interpretation of the literature.

In a systematic review from 2004, in eight studies including 642 infants presenting with ALTE, the most common clinical diagnosis, at 35%, was GOR [3]. PUNTIS and BOOTH [26] questioned these findings, as six of the eight studies did not have pH impedance studies and in the absence of confirmation of low oesophageal pH, they wondered whether those children may have had physiological GOR rather than GORD. It was concluded that demonstration of a significant temporal relationship between lower oesophageal pH and apnoea was crucial in establishing a causative relationship [27].

Evidence for GOR as a cause of ALTE/BRUE

In 1989, SEE *et al.* [23] compared 16 infants with ALTE and six control infants who solely had clinical GOR, and used prolonged pH studies in conjunction with pulse oximetry and transthoracic impedance pneumocardiography. Despite the absence of vomiting in 14 out of 16 patients with ALTE, the incidence of GOR was similar in ALTE compared to the control group (95% *versus* 100%). There was a significant drop in arterial oxygen saturation (<90% for >3 min) noted in 14 out of 16 patients with ALTE compared with no desaturation in the control group. It was observed that 54 out of the 60 desaturation episodes commenced within 3.9±0.4 min

Table 1 Summary of 12 studies examining relationship between GOR and ALTE, in date order

First author, year [ref.]	Study population size and classification	Investigation	Study type	Outcome	Comments
MACCHINI, 2017 [16]	n=41 41 infants, mean age 6 weeks At least one ALTE, and typical GOR symptoms No controls	Cardiorespiratory monitoring and pH impedance studies	Prospective Observational Follow-up with monthly clinical and cardiorespiratory monitoring	GORD in 80% of enrolled patients (moderate in 54%, severe in 27%) Significantly longer time taken for cardiorespiratory monitoring to normalise in cases of moderate-to-severe reflux ($p<0.0001$ between mild and moderate-to-severe group and $p<0.05$ between moderate and severe group)	6 patients <30 weeks' gestation 8 very low birth weight (<1500 g) Authors recommended investigating for GORD in ALTE and treating with anti-reflux therapy to prevent new episodes of ALTE
BLASCO-ALONSO, 2014 [17]	n=39 Infants admitted with ALTE No controls	MII and pH studies	Prospective, over 3 years	MII and pH studies combined: GOR found in 33 (84.6%) pH study alone: 14 (35.9%) diagnosed as GOR (8 mild, 4 moderate, 2 severe) pH monitoring: 2692 episodes of GOR identified MII: 3219 episodes of reflux identified	Addition of MII to pH-impedance study increases the diagnostic yield by detecting alkaline and weakly acidic reflux Study confirmed presence of GOR in patients admitted after ALTE; it did not evaluate any link between GOR episode and either apnoea or ALTE
KADER, 2014 [14]	n=40 Infants with GOR, mean age 125 days, mean gestation 28.5 weeks	MII-pH impedance study	Retrospective data review	9 out of 40 (22.5%) showed evidence of GOR but apnoea was only seen in one patient and ALTE was not seen	Authors concluded that GOR is less likely to be a cause of desaturation, apnoea or ALTE
SEMMEKROT, 2010 [15]	n=110 Infants diagnosed with ALTE at secondary and tertiary paediatric units No controls	Retrospective note review of clinical diagnosis	Retrospective survey over 1 year	Clinical diagnosis of GOR in 37.3% of cases	29.5% were pre-term and 8.2% were term Recurrent ALTE in 10% of patients Not able to suggest any temporal association of causality

(Continued)

Table 1 (Continued)

First author, year [ref.]	Study population size and classification	Investigation	Study type	Outcome	Comments
COHEN SABBAN, 2009 [18]	n=58 Infants with ALTE, median age 2 months No controls	3-min interval during 24-h pH impedance study to establish a temporal relationship between GOR episode and ALTE	Prospective, over 4 years	31 patients positive with 70 apnoeas/GOR events; apnoeas seen before GOR episode in 34.2% (70.8% non-acidic), during GOR in 32.8% (65.2% non-acidic) and after GOR in 32.8% (43.4% non-acidic) In 18 patients who experienced more than one episode of apnoea during monitoring, a different temporal relationship with GOR was observed at each episode	For infants in whom a temporal relationship between GOR and apnoea was observed, there was no definite pattern Authors concluded that ALTE and GOR are likely to be concurrent events and not cause-and-effect
CENDÓN, 2008 [19]	n=16 Infants with diagnosis of ALTE, median age 3.04 months No controls	MII and pH impedance studies	Prospective	Four episodes of apnoea were noted in one patient, related to GOR	Authors did not find greater rate of GOR in patients with diagnosis of ALTE compared to general population Only one patient had an association between GOR and apnoea
SEMENIUK, 2007 [20]	n=264 Children aged 4-102 months (mean±SD 20.78±17.23 months) of both sexes, with symptoms suggestive of GOR Subgroup of 8 children aged up to 2 years (mean±SD 10.00±2.78 months) of both sexes, with symptoms suggestive of ALTE, were selected from the group	24-h oesophageal pH monitoring for acid GOR diagnosis Radiography of oesophagus with barium swallow to evaluate the height of GOR “Immunoallergologic” tests to differentiate acid GOR as primary or secondary to food allergy	Prospective	From among 264 examined children who underwent 24-h oesophageal pH monitoring, acid GOR was confirmed in 170 (64.4%), and ALTE in 8 (4.8%)	Primary and secondary GOR were defined as the causative factors of ALTE in 8 (4.8%) examined infants Older children were studied, up to the age of 2 years
Mousa, 2005 [21]	n=25 Children with apnoea or ALTE, age 1-19 months No controls	Simultaneous pneumography, oesophageal pH-monitoring and MII	Prospective	Of 527 total apnoeic episodes, only 80 (15.2%) were temporally linked to GOR: 37 (7.0%) with acid reflux and 43 (8.2%) with non-acid reflux	Authors did not find any significant correlation between apnoea and frequency or duration of reflux episode, either with total reflux, non-acid or acid reflux

(Continued)

Table 1 (Continued)

First author, year [ref.]	Study population size and classification	Investigation	Study type	Outcome	Comments
McGOVERN, 2004 [3]	8 studies involving 643 infants who presented with ALTE, age 0–13 months No controls	Reviewed the most likely diagnosis in infants with ALTE	Systematic review	The most common diagnosis was GOR (n=227)	There is a wide range of diagnoses reported after ALTE; GOR was found to be the most common assigned diagnosis Clinical diagnoses attributed by admitting clinician
WENZL, 2001 [13]	n=22 Infants with symptoms of recurrent regurgitation and apnoea No controls	Simultaneous pH studies, MII, oronasal airflow and chest wall movement measurement	Prospective	364 GOR episodes were recorded by MII 165 apnoeas were documented by visual validation of polygraph records 49 apnoeas (29.7%) were associated with GOR; 11 (22.4%) of these showed acid reflux (pH <4)	A significant correlation between the time spent apnoeic and GOR was found (p<0.001); there is marked association between apnoea and GOR in infants
DABADIE, 1993 [22]	n=147 Four groups of infants under 12 weeks of age: 1) 37 infants with ALTE 2) 45 with ALTE and vomiting 3) 33 with solely gastrointestinal symptoms 4) 32 SIDS siblings	pH-impedance studies including 12 nocturnal hours	Prospective	Mean duration of nocturnal episode of reflux was higher in group 1 compared to groups 2 and 3 but didn't appear to relate to a history of ALTE	Nocturnal pH data profile failed to show a relationship between GOR and ALTE
SEE, 1989 [23]	n=22 16 infants with ALTE 6 controls manifesting clinical GOR	Simultaneous prolonged pH-impedance studies, pulse oximetry and transthoracic impedance pneumocardiography	Prospective	Despite absence of vomiting in 90% of patients with ALTE, the incidence of GOR was similar in both groups Desaturation <90% for >3 min observed during 60 episodes in 90% patients with ALTE 54 out of 60 episodes occurred within 4 min of pH falling to <4.0	Authors concluded that unsuspected (occult) GOR is common in infants presenting with ALTE and, in these patients, GOR may be directly associated with hypoxaemic episodes

(mean \pm SD) of onset of drop in oesophageal pH to <4 . They concluded that GOR is common in infants presenting with ALTE and, in these patients, GOR may be directly associated with reflex hypoxaemic events [23]. GOR was similar in both groups; the desaturation was more common in the ALTE group. This may represent a different physiological process rather than being related directly to the GOR.

WENZL *et al.* [13] found significant correlation between the time spent apnoeic and GOR in 22 infants. The aim of this study was to investigate the temporal association of apnoea and GOR with the pH-independent MII technique. Infants with recurrent regurgitation or respiratory symptoms suggestive of apnoea were investigated simultaneously with MII, pH monitoring and polysomnography. MII patterns, pH study, oronasal air flow and chest wall movement were recorded and analysed. In 22 infants, 364 GOR episodes were recorded by MII. 165 apnoeas were documented by visual validation of polygraph records. 49 apnoeas (29.7%) were associated with GOR; 11 (22.4%) of these showed acid reflux (pH <4). A significant correlation between the time spent apnoeic and GOR was found ($p<0.001$). Their conclusion was that there is marked association between apnoea and GOR in infants.

Evidence against GOR as a cause of ALTE/BRUE

In 1993, DABADIE *et al.* [22] looked for a relationship between GOR and apnoea in 147 infants aged ≤ 12 weeks. A 24-h pH impedance study was performed in four groups: 1) 37 infants who presented an ALTE; 2) 45 infants with an ALTE and chronic digestive symptoms (recurrent vomiting); 3) 33 infants with digestive symptoms only; and 4) 32 SIDS siblings. The percentage duration of oesophageal pH <4 was measured during 24 h and 12 nocturnal hours (20:00–08:00 h). In addition, the mean duration of nocturnal episodes of reflux (MDNR) was calculated (duration of pH <4 per 12 nocturnal hours divided by the number of reflux episodes). No significant difference was found in the four groups for percentage duration of oesophageal pH <4 . Nocturnal reflux was present in all groups (40% in group 1, 55% in group 2, 49% in group 3 and 63% in group 4). The MDNR was higher in group 1 (12.3 \pm 7.8 min) *versus* group 2 (6.8 \pm 5.1 min) and group 3 (6.7 \pm 3.2 min) ($p<0.05$). High MDNR did not appear to be related to a history of ALTE, since the MDNR in group 2 was identical to group 3. The nocturnal pH impedance profile failed to show a relationship between GOR and ALTE.

Mousa *et al.* [21] did not find significant correlation between apnoea (using an apnoea definition of 10 s) and frequency or duration of reflux episode, either with total reflux, non-acid or acid reflux using pH impedance. In 25 infants with an ALTE history and 527 total apnoeic episodes,

only 80 apnoeic episodes (15.2%) were temporally linked to GOR: 37 (7.0%) with acid reflux and 43 (8.2%) with non-acid reflux.

In 2008, CENDÓN *et al.* [19] examined 16 infants with a diagnosis of ALTE who underwent pH impedance studies and found no correlation between ALTE and GOR. Another larger prospective study by COHEN SABBAN *et al.* [18] focused on the 3-min interval on 24 h pH/MI monitoring when an episode of GOR happened within 3 min of an apnoea, to see if the apnoea occurred before, during or after an episode of GOR. Out of 58 infants evaluated, 31 were positive, with 70 apnoea/GOR events recorded. The percentage of apnoeas seen before a reflux episode was 34.2% (70.8% non-acidic), during GOR was 32.8% (65.2% non-acidic) and after GOR was 32.8% (43.4% non-acidic). In 18 patients who experienced more than one episode of apnoea during the recording, a different temporal relationship was observed between apnoea and GOR each time. The authors concluded that GOR and ALTE are just concurrent events without any temporal relationship between the two [18]. Similar findings were reported by KADER *et al.* [14] when they retrospectively reviewed case notes and data of pH impedance studies in infants with clinical GOR. They found that nine (22.5%) out of 40 patients had evidence of GOR but apnoea and ALTE was present in only one patient in the study cohort, and concluded that an association between GOR and apnoea/ALTE is less likely.

In 2014, BLASCO-ALONSO *et al.* [17] confirmed that the addition of MII to traditional 24-h pH monitoring increases the diagnostic yield of GOR in patients with ALTE. It was inconclusive regarding the association with ALTE as the study did not investigate whether this high occurrence of GOR was a mere coincidence or there indeed was any association of causality. This was a prospective study of MII-pH monitoring performed on 39 infants <12 months of age admitted for ALTE over a 3-year period. There were 2692 pH monitoring episodes, with a median (interquartile range (IQR)) of 24 (15–44) episodes·patient⁻¹, 1.30 (0.80–2.60) refluxes·h⁻¹, 1 (0–4) reflux episode >5 min per patient and clearance of 1.20 (0.70–2.20) min·reflux⁻¹. With pH monitoring analysis, 14 children (35.9%) could have been diagnosed with GOR based on the classical criteria. MII identified a total of 8895 events; only 3219 among them were refluxes, with a median (IQR) of 75 (54–111) refluxes·patient⁻¹ at a rate of 1.30 (1.3–2.6) episodes·h⁻¹. With the MII-pH monitoring combination there were mean \pm SD 21.60 \pm 15.21 acid reflux episodes, 67.33 \pm 32.09 weakly acid and 3.34 \pm 7.23 non-acid, giving a final total of 33 patients diagnosed with GOR.

A more recent study published in 2017 by MACCHINI *et al.* [16] looked at 41 infants with at least one ALTE and typical GOR symptoms who underwent pH studies and monthly cardiorespiratory monitoring. They found initial

presence of GOR in 80% of patients (54% moderate, 27% severe). The authors reported that it took longer for cardiorespiratory monitoring to normalise in cases of moderate-to-severe reflux. Based on these findings they recommended investigating for GOR in all cases of ALTE and starting anti-reflux therapy to prevent recurrence of ALTE-like episodes. It is worth noting that the study population included six premature babies of <30 weeks' gestation and the number of very low birth weight babies (<1500 g) was eight. There was no direct aetiological connection established between apnoea/ALTE and GOR. SEMENIUK *et al.* [20] examined older children (aged 4–102 months) and found an association between ALTE and GOR in only 4.8% patients. SEMMEKROT *et al.* [15] found that clinical diagnosis of GOR was made in 37.3% of cases presenting with an ALTE but they were not able to suggest any temporal association of causality.

Conclusion

These cross-sectional observational studies show that, although GOR is listed as the most common

cause of ALTE, there are no strong data to support the hypothesis that GOR causes a BRUE or ALTE. There are data to show that symptoms (and MII and pH study evidence) of GOR are common in infants, and some children who have had BRUE or ALTE also have GOR. There are no clear data to suggest a temporal association of cause and effect.

One study reported that it took longer for cardiorespiratory monitoring to normalise in cases of moderate-to-severe reflux [16]. They included premature and very low birth weight babies but found no temporal association. There are other studies examining apnoea of prematurity and GOR, with the same overall conclusion that there is no temporal relationship between the two conditions [28, 29]. WENZL *et al.* [13] did find a significant association but that may have been due to study design and their definition of apnoea being of a shorter duration (5 s, compared to the standard definition of 15 s), and this was an underpowered study of 22 patients.

Therefore, we conclude that the answer to the question of whether GOR is a major cause of BRUEs or ALTEs is “No”.

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Conflict of interest

None declared.

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