A Systematic Review of the Probability of Asphyxia in Children Aged <2 Years with Unexplained Epistaxis

Philippa Rees, BSc (Hons), Alison Kemp, MBBCh, MRCP, FRCPCH, Ben Carter, PhD, and Sabine Maguire, MBBCh, MRCPI, FRCPCH

Objective To determine the proportion of children aged <2 years who have been asphyxiated presenting with epistaxis in the absence of trauma or medical explanation and to identify the characteristics of the clinical presentation indicative of asphyxiation.

Study design An all-language systematic review was conducted by searching 10 databases from 1900 to 2015 and gray literature to identify high-quality studies that included children with epistaxis aged <2 years (alive or dead) with explicit confirmation of intentional or unintentional asphyxiation (upper airway obstruction). Studies of traumatic or pathological epistaxis were excluded. For each comparative study, the proportion of children presenting with epistaxis that were asphyxiated is reported with 95% CI.

Results Of 2706 studies identified, 100 underwent full review, resulting in 6 included studies representing 30 children with asphyxiation-related epistaxis and 74 children with non–asphyxiation-related epistaxis. The proportion of children presenting with epistaxis that had been asphyxiated, reported by 3 studies, was between 7% and 24%. Features associated with asphyxiation in live children included malaise, altered skin color, respiratory difficulty, and chest radiograph abnormalities. There were no explicit associated features described among those children who were dead on arrival.

Conclusion There is an association between epistaxis and asphyxiation in young children; however, epistaxis does not constitute a diagnosis of asphyxia in itself. In any infant presenting with unexplained epistaxis, a thorough investigation of etiology is always warranted, which must include active exploration of asphyxia as a possible explanation. *(J Pediatr 2016;168:178-84)*.

Although epistaxis is a frequent and often trivial finding in children, owing predominantly to trauma, congenital disorders, nasal mucosal abnormalities, and coagulation disorders, it is extremely rare in those aged <2 years, with an incidence of up to 31 per 10 000 children.[1-4] In a landmark study, epistaxis was observed in 37% of infants who were asphyxiated using covert surveillance.[5] Consequently, epistaxis has been described as a marker of asphyxiation in very young children.[6] The challenge is to distinguish between epistaxis from benign causes and epistaxis from asphyxiation.

In the US, more than 1.25 million children experience maltreatment annually.[7] Asphyxiation is a recognized form of fatal maltreatment. Although it is associated with high morbidity and mortality, asphyxiation may present with few or no external signs.[8] Child homicide is most frequent in infancy[9]; therefore, evaluating the likelihood of asphyxiation in young children, such as those presenting with epistaxis, is of paramount importance in identifying children at significant risk of further harm or death.[8] Whether asphyxiation has occurred intentionally or unintentionally, the challenge is to find clinical indicators that asphyxiation may be associated with the child's epistaxis.

The physiological mechanism underlying epistaxis in asphyxia is complex, which has led to controversy surrounding the use of epistaxis as an indicator of asphyxia.[3,10-12] The significance of epistaxis as an indicator of asphyxiation is particularly pertinent in a legal setting, as for example in a 2000 case in England, where the expert witnesses disagreed as to the relative significance of previous epistaxis as a possible indicator of repeated imposed asphyxiation.[13] The consequences of an incorrect decision either way has significant implications for the affected family.

Individual studies have aimed to define the relationship between epistaxis and asphyxiation, but given the rarity of the problem in infancy, they are necessarily small, with a high potential for bias. This systematic review aimed to address this situation by identifying associated features of epistaxis indicative of asphyxiation in children aged <2 years.

ALTE	Apparent life-threatening event
CPR	Cardiopulmonary resuscitation
SIDS	Sudden infant death syndrome

From the Cochrane Institute for Primary Care and Public Health, Cardiff University, Wales, United Kingdom

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Methods

An all-language search was conducted of published and gray literature across 10 databases from 1900 to 2015 (**Table I**; available at www.jpeds.com). The search strategy, developed in MEDLINE Ovid, consisted of 76 key words and Medical Subject Headings (**Table II**; available at www.jpeds.com). This was adapted for other databases. Supplementary "snowballing" techniques were used to augment search sensitivity including searching non-indexed journals, searching the references of all full-text articles, and correspondence with authors of included studies when necessary for clarification of clinical or social details.

Inclusion criteria were age <2 completed years with epistaxis, encompassing live and fatal cases. Epistaxis was defined as any nasal bleeding, which included oronasal bleeding but not serosanguinous secretions in fatal cases. Asphyxiation included intentional and unintentional upper airway obstruction.[14,15] Included study designs were cross-sectional, cohort, and case series with at least 3 cases (**Table III**; available at www.jpeds.com). Exclusion criteria included traumatic epistaxis or medical conditions that predispose to epistaxis, oral bleeding, case reports, review articles, expert opinion, studies in which adult and child data could not be separated, methodologically flawed studies, studies that used the presence of epistaxis to confirm asphyxiation, and studies that addressed epistaxis only in the absence of asphyxiation.

Data were extracted under the following headings: ascertainment, study population, clinical characteristics/presentation, coexistent injuries, past or subsequent medical histories, sibling medical histories, confirmation of asphyxiation, exclusion of asphyxiation, and exclusion of trauma and organic disease (**Table IV**).

Studies were assessed for inclusion, reviewed, and critically appraised independently by 2 reviewers, and disagreements were resolved by third reviewer arbitration. Studies were evaluated using a standardized critical appraisal tool that included 10 domains (**Figure 1**; available at www.jpeds.com).[20,21] This review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[22] A ranking of asphyxiation confirmation and exclusion was designed to minimize circularity, that is, to exclude studies that used the presence of epistaxis to confirm asphyxiation, and to exclude studies that did not adequately detail how asphyxiation was confirmed or excluded in a child with epistaxis (**Table V**). Only studies with an asphyxiation ranking between 1 and 3 were included. This required asphyxiation to be witnessed or admitted by the perpetrator, or to be determined by multiagency child protection groups, postmortem, sudden death investigations, or legal panels.

Data Analyses

We compared children who had adequate confirmation of asphyxia and epistaxis with children who had epistaxis but had not been asphyxiated (**Table V**). The proportion of children presenting with epistaxis who had been asphyxiated, along with the associated 95% CI, was calculated for each study. When 2 publications from the same study were identified, we approached the authors to identify duplicate cases, which were removed from the analysis to prevent double-counting. We calculated the proportion of children with epistaxis who had been asphyxiated, and also performed a descriptive analysis of the associated features of children with asphyxiation-related epistaxis.

Results

Out of the 2706 articles identified, 7 articles (6 studies) were included, representing 30 young children with asphyxiation-related epistaxis and 74 children with non–asphyxia-related epistaxis (**Table IV** and **Figure 2**; **Figure 2** available at www.jpeds.com).[2,4,5,16-19] Children with non–asphyxia-related epistaxis and concurrent upper respiratory tract infection that was not considered a definitive medical cause of epistaxis, as confirmed by the authors when necessary, were included.[4,19] Two publications from the same study were clarified with the authors to avoid duplication of cases for statistical analysis.[4,19]

Included studies were cross-sectional and case-series designs, largely recorded by covert surveillance, autopsy reports, death scene investigations, and medical records.[2,4,5,16-19]

There was no clear differential presentation of age between those with asphyxiation-related epistaxis and those with non–asphyxia-related epistaxis (**Table VI**; available at www.jpeds.com). Children with asphyxiation-related epistaxis (n = 30) were aged 30 to 684 days (1 child aged >1 year), and those with non–asphyxia-related epistaxis (n = 74) were aged 10 to 398 days (1 child aged >1 year). Age ranges were affected by the various studies' inclusion criteria (**Table IV**). Only 14 of 49 live children with epistaxis were recorded as undergoing clotting investigation.[2,4,5,16-19]

Of the 6 included studies,[2,4,5,16-19] 3 were comparative[2,4,17,19] (ie, included 2 groups of children, 1 group with epistaxis with asphyxia and 1 group with epistaxis without asphyxia), and thus provided estimates of the proportion of children presenting with epistaxis who had been asphyxiated, which was between 7% and 24% (**Table VII**). Krous et al reported a proportion of 16.7% (95% CI, 7%-36%), McIntosh et al reported a proportion of 24% (95% CI, 12%-43%), and Paranjothy et al reported a proportion of 7.1% (95% CI, 1%-32%).

Of the 30 children who were asphyxiated, 17 presented alive, aged 30 to 684 days (1 child aged >1 year), and 13 were dead on arrival, aged 32 to 324 days (**Table IV**). Reported mechanisms of asphyxiation included overlaying, positional, and mechanical asphyxiation with clothing, bedding, and hands.

The clinical presentation of the 17 live children who were asphyxiated was adequately described by 3 studies in 4 publications.[4,5,16,19] There was variability in the features described in these children (**Table IV**), with some presenting as pale,

Table IV. Details of included studies in systematic review, recording live children presenting with epistaxis who had been asphyxiated

Author, and country	Year	Design	Aims	Number children who were asphyxiated with epistaxis (fatal/live; age range)	Rank of confirmation of asphyxiation (how confirmed)	Presentation of live children and coexistent injuries					
						Skin color	Respiratory symptoms	Heart rate	Chest X-ray signs	Other	Sibling histories
Southall et al,[5] UK	1997	Case series	To describe historic markers and clinical observations of life-threatening child abuse as diagnosed using CVS	8 (live; 30-350 d old)	1 (observed on CVS)	2 pale 4 cyanotic	1 needed intubation	1 tachycardic 1 bradycardic	1 pneumothorax and pneumomediastinum	1 sweaty 1 shock 1 acidotic 1 petechiae 1 seizures	1 sibling death labelled SIDS also had nasal bleeding and a history of seizures and hematemesis 1 step sibling had a history of ALTEs and subsequently died from intentional suffocation 3 siblings had inflicted burns including 1 shoulder scald (9% burn) 2 siblings had failure to thrive 2 siblings had head injuries Other signs include facial injuries, oral injuries from force feeding, and bruising 1 sibling presented with acetaminophen ingestion
Becroft and Lockett,[16] New Zealand	1997	Case series	To describe and review the characteristics of lung sections taken from asphyxiated infants and SIDS cases	4 (live and fatal; 42-304 d old)	1 (perpetrator admission and criminal conviction for murder and attempted murder)	1 blue	1 dyspneic and grunting 1 apneic	-	1 aspiration	2 varying consciousness	1 sibling murdered by mother, had an oral bleed prior to fatal event
Krous et al,[17] US	2001	Case series	To determine the frequency of ONH in SIDS and other sudden infant deaths	4 (fatal; 40-319 d old)	1 (clinical, scene, and postmortem investigations)	-	-	-	-	-	-
Krous et al,[18] US	2007	Case series	To compare pulmonary hemorrhages in cases of SIDS and asphyxiated infants	7 (fatal; 32-324 d old)	1 (clinical, scene, and postmortem investigations)	-	-	-	-	-	-
McIntosh et al,[4,19] UK	2007 and 2010	Cross-sectional	To estimate the incidence of ONH and suffocation in infancy and to investigate their etiology and overlap	6 (live; 58-684 d old)	3 (pediatricians independently noted children with potential asphyxiation using medical records)	2 mottled 2 pale 3 blue	1 needed oxygen 2 needed intubation 1 tachypnea 1 apneic	2 bradycardic	2 patchy 1 atelectasis 1 bilateral opacities	2 capillary refill time ≥ 5s 2 acidosis 1 varying consciousness 1 petechiae 1 facial bruise	-

(*continued*)

Table IV. Continued

Author, and country	Year	Design	Aims	Number children who were asphyxiated with epistaxis (fatal/live; age range)	Rank of confirmation of asphyxiation (how confirmed)	Presentation of live children and coexistent injuries: Skin color	Respiratory symptoms	Heart rate	Chest X-ray signs	Other	Sibling histories
Paranjothy et al, UK[2]	2009	Cross-sectional	To estimate the incidence and describe the etiology of epistaxis in infants	1 (live; <56 d old)	3 (child protection process)	-	-	-	-	1 hypoxic-ischemic changes on MRI	-

CVS, covert video surveillance; *MRI*, magnetic resonance imaging; *ONH*, oronasal hemorrhage.
Asphyxiation refers to intentional and unintentional upper airway obstruction.

sweaty, and tachycardic and others presenting as lifeless, bradycardic, shocked, and acidotic, possibly related to the severity of insult or timing of presentation.[4,5,19] Children presented with skin color changes (pallor or cyanosis), respiratory and cardiac symptoms, and chest radiograph abnormalities (eg, opacities, patchiness without associated upper respiratory tract infection, pneumothorax, pneumomediastinum) characteristic of asphyxiation (Table IV).[4,5,19] Some children with abnormal pallor or respiration were also acidotic on presentation (n = 3) and had a capillary refill time ≥5 seconds (n = 2), with tachycardia (n = 1) or bradycardia (n = 3). A few live children who were asphyxiated were reported to have coexistent injuries that included petechiae of the head and neck (n = 2),[5,19] facial bruising (n = 1),[19] and hypoxic-ischemic changes on magnetic resonance imaging (n = 1).[2]

Three studies described children with epistaxis who presented dead on arrival with confirmed asphyxia (n = 13).[16-18] Postmortem signs in the children who were asphyxiated included intrapulmonary hemorrhage (n = 10/11—this was not specified for two cases) and intrathoracic/pleural petechiae (3 of the 13 children had these petechiae, four did not, and it was not possible to extract this information for the remaining 6 cases). However, petechiae were present in the children who were not asphyxiated as well. These were identified and quantified histologically on hematoxylin and eosin–stained lung sections.[16-18]

In the studies where previous and subsequent medical histories were described, repeated presentations were typical and varied (Table IV). One study described 4 children with asphyxiation-related epistaxis who had previous hospital admissions for apparent life-threatening events (ALTEs).[16] Similarly, in a study reported by Southall et al,[5] all 8 children undergoing covert video surveillance had a history of recurrent ALTEs as a prerequisite for inclusion in the study. The frequency of these ALTEs per infant ranged from 5 to 10. Two children experienced respiratory difficulties during or after ALTEs. One parent was observed fracturing the ulna and radius of an infant with a history of ALTEs and associated epistaxis. Four children who were asphyxiated presenting with epistaxis included in this review had recurrent epistaxis, defined as additional previous or subsequent history of epistaxis. One of these previous incidences of epistaxis was associated with "near-miss" sudden infant death syndrome (SIDS).[4,5]

Sibling medical histories were varied (Table IV). Three children who were asphyxiated had siblings who had died; 2 of these deaths were previously classified as SIDS.[5,16] The death of 1 sibling with oral bleeding, originally classified as SIDS, was later deemed to have been a homicide.[16]

Non–asphyxia-related epistaxis was described for 32 live children, although the clinical presentation of these children was rarely described.[2,4,17-19] Four of these 32 children presented with ALTEs, including apnea, irritability, and abnormal pallor.[19]

All 42 deceased children with non–asphyxia-related epistaxis underwent postmortem forensic investigation and

Table V. Ranking of confirmation of intentional or unintentional asphyxiation (defined as upper airway obstruction) in children presenting with epistaxis (studies ranked 1 to 3) and ranking of exclusion of intentional and unintentional asphyxiation in children presenting with epistaxis (studies ranked A to B2)

Ranking	Criteria used to confirm intentional asphyxiation	Criteria used to confirm unintentional asphyxiation
1	Intentional asphyxiation confirmed at case conference or strategy meetings or SUDI review/PRUDiC process or civil or criminal court proceedings or admitted by perpetrator or independently witnessed or confirmed at postmortem	Unintentional asphyxiation confirmed at or SUDI review/PRUDiC process or admitted by parent or carer or independently witnessed or confirmed at postmortem
2	Intentional asphyxiation confirmed by stated criteria including multidisciplinary assessment (social services/law enforcement/ medical) or sudden death investigation	Unintentional asphyxiation confirmed by stated criteria including multidisciplinary assessment (social services/law enforcement/ medical) or sudden death investigation
3	Intentional asphyxiation defined by stated criteria	Unintentional asphyxiation defined by stated criteria
4	Intentional asphyxiation stated but no supporting detail given	Unintentional asphyxiation stated but no supporting detail given
5	Suspected intentional asphyxiation	Suspected unintentional asphyxiation
Ranking	**Criteria used for active exclusion of intentional and unintentional asphyxiation from control group**	
A	By multidisciplinary assessment or child protection clinical investigation or forensic recreation of the scene or sudden death investigation	
B1	By checking either the child abuse register or records of previous maltreatment	
B2	By confirmation of organic disease or witnessed causes of epistaxis that are not asphyxiation-related	
C1	Stated but no detail given	
C2	No attempt made to exclude asphyxiation	

PRUDiC, Procedural Response to Unexpected Deaths in Childhood; *SUDI*, Sudden Unexplained Death in Infancy.

scene recreation.[17,18] Most deceased children with non–asphyxia-related epistaxis (n = 41/42) were classified as having SIDS, some were bed-sharing (n = 9), and they were found supine (n = 6) and prone (n = 4).[17,18] Epistaxis occurred before (n = 11), after (n = 9), and in the absence of (n = 1) cardiopulmonary resuscitation (CPR) in this group. Pulmonary hemorrhage, of all grades, was frequently described for cases of SIDS (n = 38/42). No coexistent signs or injuries were described, except for 1 case of bronchopneumonia.[17,18]

Discussion

Despite the rarity of epistaxis in children aged <2 years, this review reiterates its association with asphyxiation, whether intentional or unintentional. Our findings confirm that young children do experience asphyxiation-related epistaxis, and estimate that between 7% and 24% of children presenting with epistaxis in the absence of trauma or medical causes have been asphyxiated. This review also underscores that detection of these children can be difficult.

Table VII. Comparative studies providing estimates of the proportion of children presenting with epistaxis that have been asphyxiated

Study	Year	Design	p/n	% (95% CI)
Krous et al[17]	2001	Comparative case series of deceased children with ONH who both had and had not been asphyxiated	4/24	16.7 (7-36)
McIntosh et al[4,19]	2007 and 2010	Comparative cross-sectional study of live children with epistaxis who both had and had not been asphyxiated	6/25	24 (12-43)
Paranjothy et al[2]	2009	Comparative cross-sectional study of live children with epistaxis who both had and had not been asphyxiated	1/14	7.1 (1-32)

n, total number of children with epistaxis; *p*, number of children with epistaxis who were asphyxiated.

A proportion of live children who were asphyxiated presented unwell with altered skin color, respiratory difficulty, and chest radiograph abnormalities, and a proportion had no reported signs of asphyxiation. However, in comparison, most live children who were not asphyxiated had no presenting signs and symptoms described other than epistaxis, despite examination and investigation. The past medical history, concurrent signs and injuries, and family histories of deceased children with non–asphyxia-related epistaxis were poorly described; the majority of these cases were classified as SIDS.

The finding of a clear association between epistaxis and asphyxiation in infants is supported by several studies, which did not meet this review's strict inclusion criteria.[10,23-25] Meadow[23] analyzed 70 cases of child homicides (which included data from Southall et al[5]) 39% of these children who were asphyxiated had frank blood in the mouth, in the nose, or on the face. Others noting this association classified children with epistaxis as at high risk for previous asphyxiation, but there was considerable circularity; epistaxis was a criterion used to classify the risk of asphyxiation.[24]

Most live children who were asphyxiated included in this review presented with ALTEs, changes in skin color, or respiratory difficulty; however, some presented without any additional signs and symptoms, other than epistaxis. A symptomatic presentation is supported by a case report of perpetrator-admitted asphyxiation, describing an infant presenting as irritable, acidotic, and in respiratory difficulty requiring oxygen and with chest radiograph changes.[26]

The significance of epistaxis in infants, even in the absence of coexistent signs or symptoms, was highlighted by Walton et al,[10] who reported a case of an apparently well 19-day-old

baby with bilateral epistaxis discharged from the emergency room without senior review, who returned with multiple suspicious fractures.

Given the rarity of the condition under review, our findings are limited by the paucity of large-scale, high-quality comparative studies addressing this question. The nature of systematic reviews conducted to determine clinical associations means that observational studies, such as those included in our review, are the sole source of high-quality evidence in this field.[27] Unfortunately, the included studies are thus at high risk of bias enhanced by the lack of a gold standard test for intentional asphyxiation, if relevant. In addition, the information presented was often incomplete, for example, lack of details on coagulation screening. We included children who received CPR, given that the quality of CPR in the community is variable and often inadequate.[28]

We included live and dead children, although the significance of epistaxis in relation to asphyxiation may vary between these populations. The application of our quality standards enhanced the validity of findings, but limited the studies eligible for inclusion.

The American Academy of Pediatrics has stated that numerous circumstances can indicate intentional asphyxiation, including recurrent cyanosis, apnea, or ALTEs in the care of the same person; age >6 months at death; an unexplained or unexpected sibling death; simultaneous or near-simultaneous death in twins; deaths of infants under the care of the same unrelated person; and evidence of pulmonary hemorrhage.[29] Our findings support most of these recommendations, but this review found insufficient evidence to be categorical about associated features.

Any child aged <2 years presenting with epistaxis, in the absence of witnessed trauma or a clear medical cause, should receive a full clinical assessment to explore the possibility of asphyxiation or occult trauma, in addition to organic causes. This presentation warrants a full investigation, including a complete examination and review by an otolaryngologist, coagulation screening, and a comprehensive family and social history. In addition, these children should be investigated for suspected maltreatment in line with the standard recommendations for this age group, which would include skeletal surveys and head imaging in those aged <1 year and skeletal scans for those aged 1-2 years.[30] ■

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Reprint requests: Dr Sabine Maguire, MBBCh, MRCPI, FRCPCH, Cochrane Institute of Primary Care and Public Health, School of Medicine, Cardiff University, Cardiff, Wales, UK, CF14 47S. E-mail: sabinemaguire@gmail.com

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Visual Disturbances in Cystic Fibrosis following Chloramphenicol Administration

Huang NN, Harley RD, Promadhattavedi V, Sproul A. J Pediatr 1966;68:32-44

Nancy Huang (pulmonologist), Rob Harley (ophthalmologist), and others from St. Christopher's Hospital for Children report the novel occurrences of optic neuritis or retrobulbar neuritis in 9 of 33 patients receiving chloramphenicol in late stages of cystic fibrosis. The cases are described perfectly: drug doses, long durations of therapy, symptoms of visual loss, retinal abnormalities, and improved courses after discontinuation of drug, with or without vitamin B complex administration. How frequently in medical science does the early report of a condition include the description, hypothesis of pathophysiology, experiential observation of proof of concept, and then path to resolution? The authors observed in their conclusions, as open-minded scientists, that these cases of optic neuropathy could be due to drug toxicity, drug hypersensitivity, or drug-associated vitamin deficiency. This was a time when chloramphenicol was used eagerly, and with knowledge of idiosyncratic bone marrow suppression, as a lifesaving treatment for children with *Hemophilus influenzae* type b meningitis and other serious antibiotic-resistant infections.

This writer had the privilege of working with Dr Huang and Dr Harley at St. Christopher's in the 1970s. Dr Huang had amassed a population with cystic fibrosis of well over 300 patients. There never was a time in the 1970s without one of her terminal middle-school patients in the hospital. Younger affected siblings observed what would be their fate and parents mourned loss of more than 1 child after their prolonged painful deterioration.

Nancy Huang was their hero. Standing at 5 feet on a tall day, she had a constant wide smile and sparkling eyes and the fierce fight of a mother bear for her cubs. As a trainee in infectious diseases, sharing a train ride with Dr Huang to Washington, DC for the annual Interscience Conference on Antimicrobial Agents and Chemotherapy antibiotic meetings, this writer remembers vividly 2 conversations. In the first, she told me that she was going shopping at ICAAC for a new antibiotic to help her sick patients. In another, I learned that she did relax, treating herself to gardening for 45 minutes every single Sunday. Married to Peter Kuo, MD, a ground-breaking lipid scientist at the University of Pennsylvania, this couple literally dedicated their lives to science and service, and had enormous impact not only on science and suffering but on countless trainees such as me.

Sarah S. Long, MD
Department of Pediatrics
St. Christopher's Hospital for Children
Philadelphia, Pennsylvania
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Cardiff Child Protection Systematic Review Group

CORENT: Child prOtection Review Ear Nose & Throat

Reviewer's name:		Date:	

Critical appraisal form

Author(s):

Title:

Journal reference:

Identifier:

Section A.

	Study Type: Please tick study type	Yes
1	Prospective Cohort Study	
2	Retrospective Cohort	
3	Cross-sectional Study	
4	Case Control Study	
5	Case Series	
6	Case Report	

Section B.

Key Question: please tick which question this study addresses. **If the study does not meet the inclusion criteria and it should be EXCLUDED.**	**Yes**	**Comment**
1. What are the distinguishing characteristics of epistaxis in a child, in the absence of direct trauma to the nose, that are indicative of asphyxiation? **(include studies of children <2 years)**		
If the study addresses none of the questions listed above, please **EXCLUDE** (**If study is excluded go to the end of critical appraisal form)**		

Figure 1. The critical appraisal form used to review all full text articles. *(Continues)*

Section C.

Exclusion Criteria: please tick any of the following criteria which apply	Yes	Comment
Formal consensus / expert opinion / personal practice / review article		
Adult only data OR mixed adult & child data, where child data cannot be isolated		
Management of injury papers		
Oral injury		
Fractures		
Burns to throat or external nose		
Bruising alone		
Studies of complications or outcomes of abusive ENT injury		
Injuries as a result of sexual abuse		
Oral bleeding only		
Study exclusively addresses epistaxis:		
Epistaxis due to any cause other than asphyxia		
Trauma (blunt or penetrating)		
Prior nasal surgery		
Findings not due to asphyxia / nasal bleeding at post mortem but not when alive		
Medical causes of epistaxis (coagulation disorder, congenital disorders, pre-existing disease)		
Case reports or case series ≤2		
If you have answered yes to any of these questions, the study should be EXCLUDED (If study is excluded go to the end of critical appraisal form)		

Figure 1. Continues.

Section D.

Additional Study Quality Criteria Required	
1. How have the authors defined asphyxiation? (please state criteria used)	
2. What investigations were performed to exclude other causes of epistaxis?	**Coagulation Screen** ☐ **Full Blood Count** ☐ **Von Willebrand Assay** ☐ **Other/ none (please state**
3.What ranking of asphyxiation criteria would you apply? **Rank 1:** Asphyxiation confirmed at case conference or strategy meetings or Sudden Unexplained Death in Infancy (SUDI) review/ Procedural Response to Unexpected Deaths in Childhood (PRUDiC) process or civil or criminal court proceedings or admitted by perpetrator or independently witnessed or confirmed at post-mortem **Rank 2:** Asphyxiation confirmed by stated criteria including multidisciplinary assessment (social services/ law enforcement/ medical) or sudden death investigation **Rank 3:** Asphyxiation defined by stated criteria **Rank 4:** Asphyxiation stated but no supporting detail given **Rank 5:** Suspected asphyxiation **Mixed** ranking	**Rank 1** **Rank 2** **Rank 3** **Rank 4** **Rank 5** **Mixed ranks – please specify** If study has a level **4-5 ranking** or is **mixed** (and relevant cases cannot be extracted) it should be **EXCLUDED** **(If study is excluded go to the end of critical appraisal form)**

Figure 1. Continues.

4. Have the authors actively excluded asphyxiation from the non-asphyxiated group? **A.** By multi-disciplinary assessment or child protection clinical investigation or forensic recreation of the scene or sudden death investigation **B1.** By checking either the child abuse register or records of previous maltreatment **B2.** By confirmation of organic disease or witnessed causes of epistaxis that are not asphyxiation-related **C1.** Stated but no detail given **C2.** No attempt made to exclude asphyxiation	**A** **B 1 or 2** **C 1 or C2** **N/A** If you have answered yes to **C1 or C2,** comparator group should be **EXCLUDED** (If study is excluded go to the end of critical appraisal form)

Section E.

Quality of nasal examination:	Comment **(if not specifically stated note here for correspondence with author)**
1. Endoscopy after decongestant 2. Examination by otolaryngologist using appropriate illumination 3. Examination by any clinician using appropriate illumination 4. No examination / no detail provided	
(If study excluded go to end of critical appraisal form)	

Figure 1. Continues.

Section F.

Methodological Quality Criteria for Comparative Studies. **Please tick the appropriate column.**	**Yes**	**No**	**Unclear**	**N/A**
1. Were the aims of the study clearly stated?				
2. Was the study clearly focused in terms of population selected, the comparative features assessed and outcomes considered?				
3. Do the authors appear to have conducted a preparatory unbiased literature review to identify current state of knowledge?				
4. Was the choice of study method appropriate?				
5. Was the comparison group appropriately chosen?				
6. Was the comparison group enrolled in the same time period and assessed in the same way as the asphyxiated group?				
7. Have the results of the study been clearly presented?				
8. Are the data in the tables or graphs and the text consistent?				
9. Were the statistical methods used appropriately?				
10. Were all important outcomes/ results considered?				

Section G.

Reviewer's Conclusions and Comments	
Key points meriting inclusion (list strengths)	

Figure 1. Continues.

Weaknesses, potential confounders and study limitations	

Section H.

Final Decision	Yes	No	Comment
Is the study included?			
If the study is excluded, should it be kept for background information, introduction or discussion?			

Section I.

Additional Comments

Figure 1. Continued.

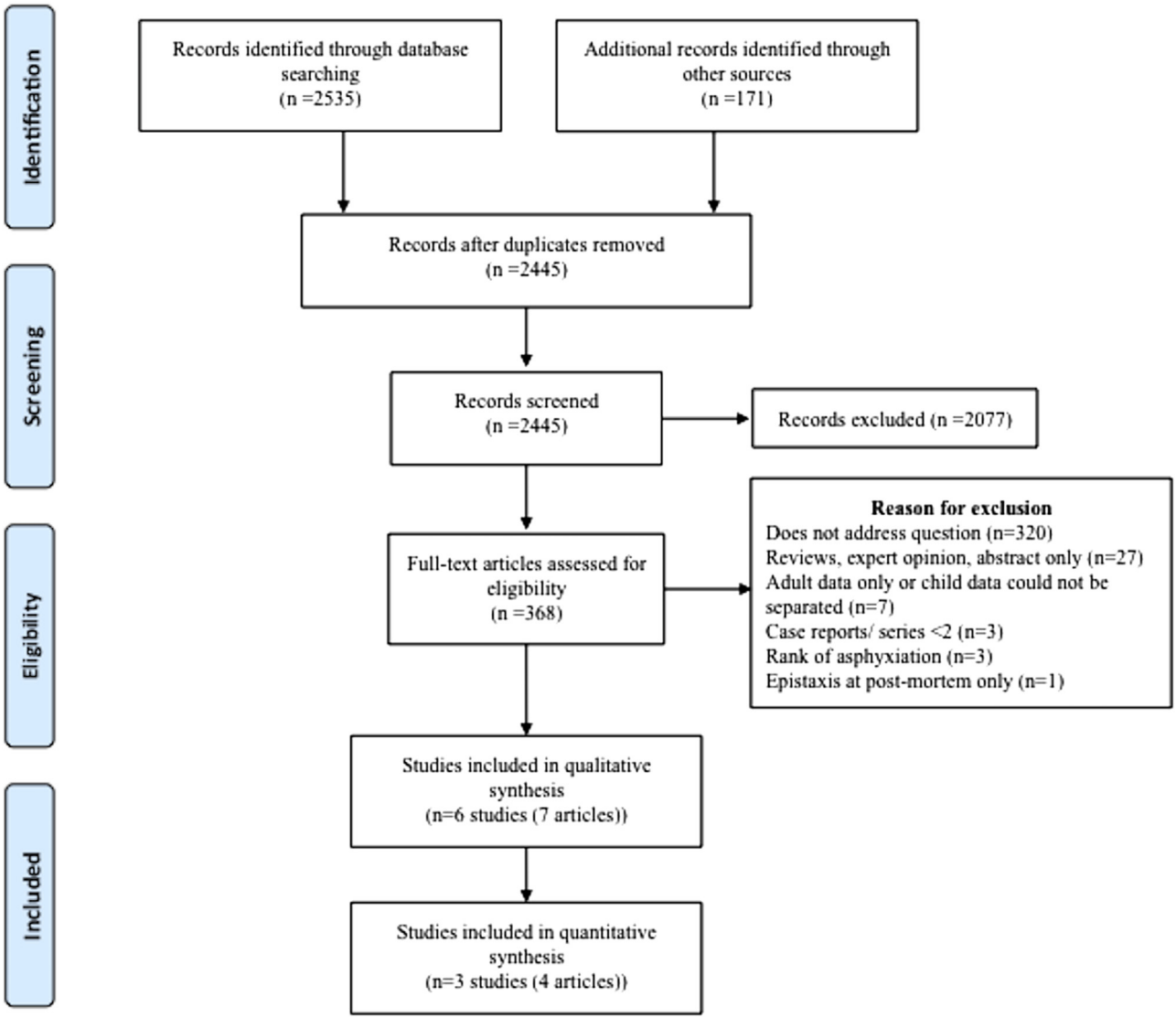

Figure 2. PRISMA flow diagram demonstrating included and excluded studies and the reasons for exclusion in the systematic review of epistaxis in relation to asphyxiation.[22]

Table I. Databases searched for systematic review of children presenting with epistaxis with or without asphyxia (intentional or unintentional upper airway obstruction)

Database searched	Search period
Cochrane Central Register of Controlled Trials	1960-2014*
EBSCO–CINAHL (Cumulative Index to Nursing and Allied Health Literature)	1960-2015
Google Scholar	Inception-2014*
Ovid–EMBASE	1947-2015
Ovid–HMIC (Health Management Information Consortium)	1983-2014*
Ovid–MEDLINE	1946-2015
Ovid–MEDLINE In-Process and Other Non-Indexed Citations	2014-2015
PubMed	2014*
Scopus	1960-2015
Web of Knowledge (science citation index expanded and conference proceedings citation index science)	1900-2015

*No yield, so search was discontinued during review update.

Table II. MEDLINE search strategy for systematic review of epistaxis in children with or without asphyxia (intentional or unintentional upper airway obstruction)

1. exp Child/
2. exp Child, Preschool/
3. exp Adolescent/
4. exp Infant/
5. Infant/or exp Infant, Newborn/
6. (child: or toddler: or baby or infant* or adolescent*:).mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Child Abuse/
9. exp Battered Child Syndrome/
10. exp Shaken Baby Syndrome/
11. exp Airway Obstruction/or exp Asphyxia/
12. (child abuse or battered child or battered baby or shaken baby or asphyxia or airway obstruction).mp.
13. suffocat*.mp.
14. asphxia*.mp.
15. nonaccidental injur*.mp.
16. non-accidental injur*.mp.
17. nonaccidental trauma.mp.
18. non-accidental trauma.mp.
19. soft tissue injur*.mp.
20. Infanticide.mp.
21. abusive trauma.mp.
22. (child maltreatment or child protection).mp.
23. (child adj3 maltreatment).mp.
24. (child adj3 physical abuse).mp.
25. child murder.mp.
26. covert homicide.mp.
27. child homicide.mp.
28. exp Munchausen Syndrome by Proxy/
29. Factitious disorder by proxy.mp.
30. Fabricat* ill*.mp.
31. Induc* ill*.mp.
32. Munchausen Syndrome by proxy.mp.
33. unnatural death.mp.
34. exp Epistaxis/
35. exp Ear/
36. exp Nose/
37. exp Pharynx/
38. (epistaxis or ear or nose or throat or pharynx).mp.
39. nosebleed.mp.
40. nose bleed.mp.
41. (bleed* adj3 nose).mp.
42. nasal hemorrhage.mp.
43. nasal haemorrhage.mp.
44. nasal bleed*.mp.
45. intra-alveolar haemorrhag*.mp.
46. intra-alveolar hemorrhag*.mp.
47. oronasal bleed*.mp.
48. oronasal haemorrhag*.mp.
49. oronasal hemorrhag*.mp.
50. otalgia.mp.
51. (otitis adj3 extern*).mp.
52. otitis media.mp.
53. pharyngitis.mp.
54. oropharynx.mp.
55. laryngopharynx.mp.
56. Otorhinolaryng*.mp.
57. Otolaryngo*.mp.
58. paranasal sinus*.mp.
59. submandibular gland*.mp.
60. parotid gland*.mp.
61. palatine tonsil*.mp.
62. (bleed* adj3 ear*).mp.
63. (caustic adj3 ear*).mp.
64. hypopharyn*.mp.
65. hypopharyn* perforat*.mp.
66. perichondritis.mp.
67. Animals/
68. animal stud*.mp.

(*continued*)

Table II. Continued

69. exp "Review"/
70. exp Child Abuse, Sexual/
71. sexual abuse.mp.
72. allerg*.ti.
73. surg*.ti.
74. congenital.ti.
75. 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74
76. cohort*.tw.
77. controlled clinical trial.pt.
78. exp Epidemiologic Methods/
79. exp Case-Control Studies/
80. (case$ and control$).tw.
81. exp case report/
82. (case$ and series).tw.
83. exp case studies/
84. exp Cohort Studies/
85. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 32 or 33
86. 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66
87. 76 or 77 or 78 or 79 or 80 or 82 or 84
88. 7 and 85 and 86 and 87
89. 88 not 75

A truncation used in Medline searches to allow retrieval of several variations of the same word, eg, suffocat—would detect suffocate and suffocation.

Table III. Inclusion and exclusion criteria for systematic review of epistaxis in children with or without asphyxia

Inclusion criteria	Exclusion criteria
Studies of all observational evidence types other than case reports (minimum 3 cases)	Personal practice
English and non-English articles	Review articles
Patients aged <2 completed years	Case reports
Epistaxis defined as any bleeding from the nose/nasal hemorrhage including ONH	Case series (<3 subjects)
Studies with a mixed population of children with epistaxis as a result of asphyxiation and not as a result of asphyxiation	Studies where the population only includes children with epistaxis in the absence of asphyxiation
Asphyxiation of any etiology (confirmation rank 1-3) defined as deprivation of oxygen from upper airway obstruction, inflicted or unintentional	Studies where the population includes adults and children and the data for children cannot be extracted
No asphyxiation (confirmation rank A-B2)	Likelihood of asphyxiation rank 4-5, or mixed rank
	Likelihood of no asphyxiation rank C1-C2
	Methodologically critically flawed papers
	Study exclusively addresses epistaxis in association with • Trauma (blunt or penetrating) • Previous nasal surgery • Postmortem examination alone • Medical causes of epistaxis (coagulation disorder, congenital disorders, preexisting ENT disease)
	Oral bleeding only

ONH, oronasal hemorrhage; *ENT*, ear nose and throat.

Table VI. Ages of children included in comparative studies that provided estimates of the proportion of children presenting with epistaxis who have been asphyxiated

Study	Year	Age <2 mo, p/x	Age 2-12 mo, p/x	Age >12 mo, p/x
Krous et al[17]	2001	1/10	3/10	NA
McIntosh et al[4,19]	2007 and 2010	4/17*	1/17*	1/1
Paranjothy et al[2]	2009	1/7	0/6	NA

NA, not applicable; *p*, number of children with epistaxis who were asphyxiated; *x*, number of children with epistaxis who were not asphyxiated.
*17 children aged <12 months in the cohorts of McIntosh et al had epistaxis in the absence of asphyxiation.