

## Chapter 2

# Post-mortem Investigation of Sudden Unexpected Death in Infancy: Role of Autopsy in Classification of Death

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**Abstract** Sudden unexpected deaths in infancy (SUDI) represent the commonest group of post-neonatal childhood deaths. Pathologists in the UK are currently recommended to follow the “Kennedy protocol” when performing such autopsies. This suggested protocol is primarily based on practice from expert opinion and the approach to the post-mortem examination has changed little over recent decades. The identification of specific medical causes of death at autopsy in SUDI has slightly improved in recent years, but around two-thirds of cases remain unexplained, being classified as SIDS or SUDI according to local protocols and circumstances. Current protocols include the autopsy with macroscopic examination of organs, but in the majority of cases in which a cause of death is identified, the diagnosis is based on a combination of ancillary investigations including histological examination and microbiological findings, which are mandatory studies in these infant deaths. However, with increasing evidence regarding the relative frequency with which the various components of the autopsy provide information regarding the cause of death, and recognition that immunological responses and/or bacterial products may be of increasing importance, alternative and/or additional diagnostic techniques are required which may result in modified evidence-based autopsy protocols. The aim of this article is to review the current evidence for protocols of post-mortem investigations of SUDI, with particular emphasis on features which may distinguish natural from unnatural deaths, and to evaluate the approach to investigations which maximise the likelihood of identifying natural causes of death. The article will not discuss issues related to non-accidental or inflicted injury, which remain complex and beyond the scope of this review.

**Keywords** Sudden infant death • SIDS • Autopsy • Microbiology • Rib fractures • Pulmonary haemosiderin-laden macrophages

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## Terminology and Classification of Sudden Infant Deaths

Sudden unexpected death in infancy (SUDI) of an apparently healthy child has been reported for thousands of years, and became commonly known as “cot-/crib-death.” This term is potentially misleading, as it implies that death invariably occurs in the cot [1] and the term was superseded by the definition of sudden infant death syndrome (SIDS) in 1969 [2]. However, “cot-death” is still widely used, particularly by the lay public, sometimes synonymously with SIDS, while others apply it to any sudden unexpected infant death, even when a cause of death is determined. SIDS was initially defined as, “the sudden death of an infant or young child, which is unexpected by history, and in which a thorough post-mortem examination fails to demonstrate an adequate cause of death” [2], and in 1971 SIDS became a registrable cause of death in England and Wales [3]. Decades later, in 1989, the National Institute of Child Health and Human Development (NICHD) proposed further modification of the definition, restricting the term to infants less than 1 year of age, and emphasising the importance of a thorough death scene investigation and review of the clinical history [4]. This was subsequently further modified into “typical” (Category I SIDS) and “atypical” deaths (Category II SIDS), as well as a third category (Category III SIDS) intended solely for epidemiological purposes to accommodate countries where autopsies were not routinely performed [5, 6], although this failed to gain wide acceptance. In 2004, an international panel [7] proposed a further classification, widely referred to as the “San Diego definition,” defined as, “the sudden unexpected death of an infant less than 1 year of age, with onset of the fatal episode apparently occurring during sleep, that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history” (Table 2.1).

This current definition restricts the diagnosis of SIDS to cases where death is associated with sleep and makes it compulsory to investigate the circumstances surrounding death [7]. It is noteworthy that according to this classification, co-sleeping and prone sleeping-associated deaths are to be classified as SIDS (either as Category I or Category II deaths depending on other findings) if there is no convincing evidence of accidental asphyxia based on the review of the death scene and/or autopsy findings, a contentious issue for many pathologists, there being an ongoing debate as to whether sudden infant deaths in the presence of such clearly established risk factors constitute SIDS, accidents or neglect [3, 9].

Several variables intrinsic to the definition also remain poorly defined. For example, what criteria constitute “sudden” and what exactly is meant by “unexpected?” Equally, there is variation in pathologists’ interpretation of the potential significance of pathological changes and whether these may represent an adequate explanation of death or whether the death would better be classified as SIDS [1, 10, 11]. Furthermore, a “complete autopsy” according to this protocol requires toxicology and vitreous chemistry, neither of which is routinely performed in many centres in the UK (*vide infra*). Finally, the term “SIDS” remains controversial in view of its

**Table 2.1** The San Diego classification of SIDS (adapted from Krous et al. [7] and Bajajowski et al. [8])

	Clinical history	Circumstances of death	Autopsy
General definition of SIDS	<ul style="list-style-type: none"><li>• Sudden unexpected death</li><li>• &lt;1 year of age</li><li>• Onset of fatal episode during sleep</li><li>• Death unexplained by clinical history</li></ul>	<ul style="list-style-type: none"><li>• Death unexplained after review of circumstances of death</li></ul>	<ul style="list-style-type: none"><li>• Death unexplained by autopsy findings</li></ul>
Category 1A SIDS: (classic features of SIDS present and completely documented)	<ul style="list-style-type: none"><li>• &gt;21 days and &lt;9 months of age</li><li>• Normal clinical history</li><li>• Term pregnancy (≥37 weeks)</li><li>• Normal growth and normal development</li><li>• No similar deaths of siblings, close genetic relatives (uncles, aunts, or first-degree cousins), or other infants in the custody of the same caregiver</li></ul>	<ul style="list-style-type: none"><li>• Death unexplained by investigation of various scenes where incidents leading to death might have occurred</li><li>• Safe sleeping environment</li><li>• No evidence of accidental death</li></ul>	<ul style="list-style-type: none"><li>• Death unexplained by autopsy findings<ul style="list-style-type: none"><li>– Radiology</li><li>– Microbiology</li><li>– Vitreous chemistry</li><li>– Metabolic studies</li><li>– Toxicology</li></ul></li><li>• No lethal pathological findings</li><li>• Minor respiratory system inflammatory infiltrates are acceptable</li><li>• Intrathoracic petechiae supportive but not obligatory or diagnostic</li><li>• No evidence of unexplained trauma, abuse, neglect, or unintentional injury</li><li>• No significant thymic stress*</li></ul>
Category 1B SIDS: (classic features of SIDS present but incompletely documented)	<ul style="list-style-type: none"><li>• As above</li></ul>	<ul style="list-style-type: none"><li>• Not performed</li></ul>	<ul style="list-style-type: none"><li>• One or more not performed:<ul style="list-style-type: none"><li>– Radiology</li><li>– Microbiology</li><li>– Vitreous chemistry</li><li>– Metabolic studies</li><li>– Toxicology</li></ul></li></ul>

(continued)

Table 2.1 (continued)

	Clinical history	Circumstances of death	Autopsy
Category II SIDS: (includes infant deaths that meet Category I criteria except for ≥1 of the following)	<ul style="list-style-type: none"><li>• Age 0–21 days or 9–12 months</li><li>• Similar death of siblings, close relatives, or other infants in the custody of the same caregiver (that are not considered suspicious of infanticide or of a recognised genetic disorder)</li><li>• Neonatal/perinatal complications (e.g. prematurity) that have resolved by the time of death</li></ul>	<ul style="list-style-type: none"><li>• Mechanical asphyxia or suffocation caused by overlaying not determined with certainty</li></ul>	<ul style="list-style-type: none"><li>• Abnormal growth and development not thought to have contributed to death</li><li>• Marked inflammatory changes or abnormalities not sufficient to be unequivocal causes of death</li></ul>
Unclassified sudden infant death	<ul style="list-style-type: none"><li>• Criteria for Category I or II SIDS not met</li></ul>	<ul style="list-style-type: none"><li>• Alternative diagnoses of natural or unnatural conditions are equivocal</li></ul>	<ul style="list-style-type: none"><li>• Alternative diagnoses of natural or unnatural conditions are equivocal, or</li><li>• Autopsy not performed</li></ul>

\*Significant thymic stress is defined as thymic weight <15 g and/or moderate or severe cortical lymphocyte depletion; occasional “starry sky” macrophages or minor cortical depletion are acceptable

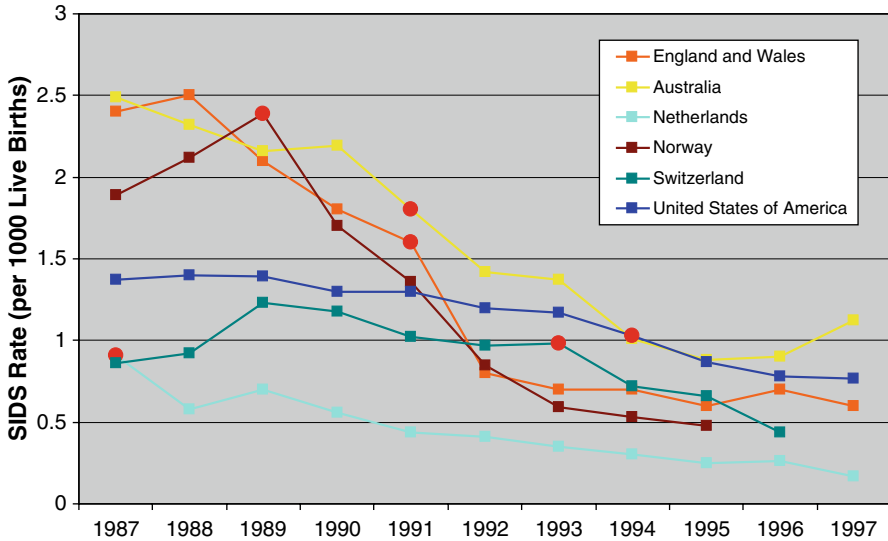
inclusion of the term “syndrome,” with some arguing that SIDS merely represents a “dustbin diagnosis” for any sudden infant death which remains otherwise unexplained [12]; however, even ardent supporters for the continued use of the term “syndrome” agree that SIDS is unlikely to constitute a single cause of death, but is likely to represent a heterogeneous group of sudden infant deaths that currently remain unexplained but which share a common mechanism(s) of death [7].

The term sudden unexpected death in infancy (SUDI), in contrast, was adopted by the CESDI SUDI study [1] and is the preferred term in the UK for the presentation of all sudden and unexpected deaths in the first year of life, including non-natural sudden deaths due to accidents and inflicted injury, although the term is usually restricted to infants aged 7 days to 1 year of age [1]. The Kennedy report [13] also uses the acronym SUDI, since all cases are initially investigated in a similar manner. If no cause of death is identified following the autopsy, the Kennedy guidelines recommend that deaths are classified as SIDS, or simply as SUDI, depending on the results of the review of the clinical history and examination of the circumstances of death; however, we prefer the term “unexplained SUDI” as a pathological classification of death if the latter remains unexplained, as there is little agreement amongst pathologists, despite published guidelines [7, 8, 13], on classifying otherwise unexplained SUDI as SIDS, particularly in the presence of co-sleeping [3]. Furthermore, the term “SUDI” merely refers to the presentation of death, which can be divided into “explained SUDI” and “unexplained SUDI” following the autops and review of the clinical history and death scene; to use “SUDI” both as presentation of death and cause of death if the latter remains undetermined, is confusing and potentially misleading. In contrast, the term “unascertained” is generally used when the pathologist identifies features in the clinical history or at autopsy that raise the suspicion of possible inflicted injury but which are insufficient to account for the death [14]. It is not recommended that the term “unascertained” be used synonymously with SIDS or unexplained SUDI, as the latter terms imply a natural cause of death, whilst the term “unascertained” includes both natural and non-natural deaths, and as a consequence, affected families may be stigmatised by designating an otherwise non-suspicious but unexplained sudden death as “unascertained” [3, 13].

## **Risk Factors for Unexplained SUDI/SIDS**

Unexplained SUDI/SIDS affects around 0.5–1/1,000 infants, with recent decline in rates, predominantly attributed to modifications based on removal of risk factors, mainly placing babies supine for sleep, with little impact from other behaviour modification strategies such as reducing smoking during pregnancy or promoting breastfeeding (Fig. 2.1) [12].

Many risk factors for unexplained SUDI/SIDS have been identified by epidemiological studies, including associations with young maternal age, low social class, high parity, multiple pregnancy, intrauterine growth restriction, prematurity



**Fig. 2.1** SIDS Rates by Country, 1987–1997 (All data taken from Byard and Krous [12], red circles indicate the year the risk reduction campaign was launched in each country)

and maternal smoking [1, 15–20]. The most important – and readily modifiable – behavioural factor appears to be prone sleeping, and to a lesser extent, side sleeping [21–25], such that public health campaigns were introduced in many countries to promote supine sleeping, leading to a dramatic decline in the incidence of SIDS (Fig. 2.1). Currently, co-sleeping or bed-sharing remains a controversial risk factor for SUDI, but most studies demonstrate a positive association, especially when co-sleeping during the first 6 months of life, if the infant was born prematurely (<37 weeks gestation) or with low birth weight (<2.5 kg), or if either parent is a smoker, has been drinking alcohol, taken drugs or other medication, or is excessively tired, with co-sleeping with an infant on an armchair or sofa being especially high risk [1, 26–31]. Sharing a sofa has been shown to carry a very high risk of SIDS: in the CESDI study [1], co-sleeping on a sofa carried an almost 23-fold greater risk of SIDS than infants not co-sleeping with an adult. In a recent systematic review, Blair et al. [32] report a significantly increased risk of SIDS in infants whose heads were covered by bed clothes (adjusted OR 17). The mechanism of death in these and co-sleeping infants remains unclear; theories include hypoxia, accumulation of carbon dioxide, hyperthermia and partial asphyxiation, and there continues to be uncertainty about how such cases should be classified, most pathologists in the UK preferring not to use SIDS in these circumstances. Conversely, several studies have shown that the use of pacifiers (soothers or dummies) significantly reduces the risk of SIDS [20], a meta-analysis demonstrating a pooled multi-variate OR of around 0.4 for pacifier use during the last sleep [33]. Interestingly, many risk factors are shared between cases of explained and unexplained SUDI, including preterm birth, young maternal age, single mothers, low socioeconomic

status, maternal smoking, and apparent mild illness in the preceding 24 h [34, 35]. However, explained SUDI deaths are generally younger or older than SIDS infants, with more explained SUDI deaths occurring in the first month of life and after 6 months of age.

The current conceptual framework linking the interactions between established epidemiological risk factors and their biological, genetic and other associations is presented as the “triple-risk” hypothesis comprising an intrinsically vulnerable infant, at a critical developmental period, and exposure to exogenous stressors [12, 36].

## Role of Infection in SUDI

Some SUDI deaths clearly demonstrate evidence of definite acute bacterial infection, such as cases with pneumonia or meningitis. However, increasing evidence also suggests that other mechanisms may implicate bacteria and/or bacterial products, or an associated abnormal host response, in some cases of currently unexplained SUDI/SIDS, although no proven mechanism has yet been established. The so-called common bacterial toxin hypothesis [37–39] postulates that some SIDS may be caused by bacterial toxins, most likely derived from upper respiratory tract organisms, present in young infants when maternal IgG concentrations are dwindling prior to maturity of the infants’ immune system, with some toxins acting as superantigens to cause massive release of cytokines with resulting toxic shock-like syndrome or septic shock, and death [38, 40]. Alternatively, it has been speculated that toxins may act directly on neural or myocyte membranes to induce sudden death [38]. It has been reported that asymptomatic nasopharyngeal carriage of *Staphylococcus aureus* in infants is more common within the first 3 months of life than in older infants [41], and significantly more common in SIDS infants  $\leq 3$  months old than in age-matched healthy controls [42]. Furthermore, it has been demonstrated that prone sleeping in the presence of an upper respiratory tract infection is associated with significantly increased bacterial carriage, including increased colonisation by staphylococci [41], and two recent retrospective studies have shown a significantly increased prevalence of *S. aureus* on post-mortem cultures of lung, blood and/or spleen in unexplained SUDI/SIDS compared to explained SUDI due to non-infective causes [43, 44]. The host response to such bacterial products may be further altered according to specific genetic polymorphisms resulting in abnormal cytokine responses [45].

Many other theories regarding the pathogenesis of unexplained SUDI/SIDS have been postulated, including exposure to immunological reactions such as hypersensitivity and/or anaphylaxis [46], impaired autonomic regulation with impaired arousal and ventilatory responses [20, 47–50], cardiac conduction system abnormalities [51, 52], and a range of neuropathological aberrations, mainly related to brainstem abnormalities, such as hypoplasia of brainstem nuclei [53, 54] and serotonergic aberrations [55–57], and even epilepsy [58], all of which are beyond the scope of this article, and at present are of little direct relevance to the pathologist, who is required to provide a probable cause of death for Her Majesty’s (HM) Coroner.

## The SUDI Autopsy Protocol and Determination of Cause of Death

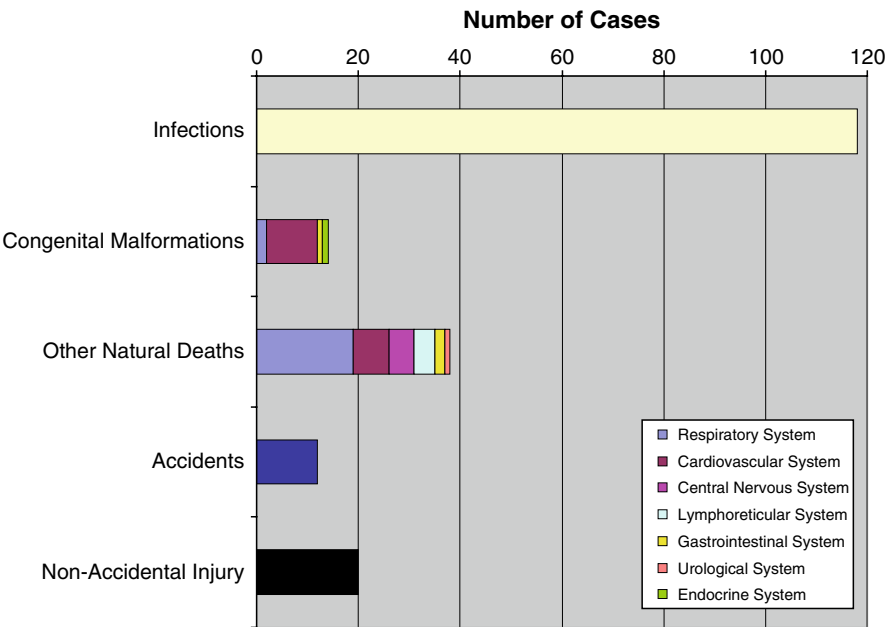
Current autopsy guidelines are primarily based on the “Kennedy Report” [13], which advocates a multi-agency approach to the investigation of all SUDI. The determination of a cause of death depends not only on the findings of the post-mortem examination, but includes a comprehensive review of the circumstances of death, including a home visit, and is dependent on the interacting roles of HM Coroner, the police, community paediatricians and other agencies such as social services. In this review, we shall focus specifically on the autopsy; according to current guidelines, the autopsy should be performed by a paediatric pathologist with training and expertise in the investigation of infant death. The autopsy in this setting not only comprises an external examination and systematic prosection, but includes a range of ancillary investigations including post-mortem radiology, histological examination, bacteriological and virological investigations, metabolic analyses for fatty acid oxidation defects, and other, more targeted and specific tests such as toxicology and biochemical assays in selected cases. Both the Kennedy autopsy protocol [13] and published international guidelines [8] recommend a variety of different investigations, although many are not evidence based, and the relative importance of these in determining cause of death in SUDI varies greatly.

In a large study at one paediatric tertiary centre in which a total of 1,516 paediatric post-mortem examinations were performed over a 10-year period, there were 546 autopsies of infants aged 7–365 days presenting as SUDI [59]. Of these, in 202 (37%) an identifiable cause of death was present following post-mortem examination (“explained SUDI”), whilst the majority (344 cases; 63%) remained “unexplained SUDI.” Of the 202 explained deaths, the majority (around 60%) were due to an infective process, most commonly pneumonia (20%), whilst non-infective causes included congenital malformations (7%), and deaths due to accidental (6%) and non-accidental (10%) injuries (Fig. 2.2). Of the infective deaths, most were due to bacterial infections (80%), with the remainder presumed viral.

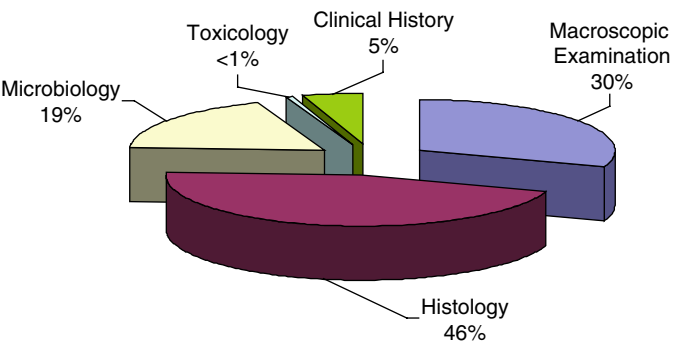
Importantly, the component of the post-mortem examination which primarily determined the cause of death was the histological examination in 92 (46% of explained SUDI, 17% of all SUDI), the macroscopic examination at the time of autopsy in 61 (30% of explained SUDI, 11% of all 546 SUDI), microbiological examination in 38 (19% of explained SUDI, 7% of all 546 SUDI) and clinical history/death scene in 10 (5% of explained SUDI, 2% of all 546 SUDI; Fig. 2.3). Radiology showed fractures in around 6% of cases, but, whilst the findings contributed to the final diagnosis in many, the presence of fractures detected radiologically did not primarily determine the cause of death in any case.

The majority of infection-related diagnoses were made primarily on histological examination, although microbiological analyses accounted for around 20% of the diagnoses which would have been missed had routine microbiological sampling not been performed. However, several investigations suggested in the current autopsy protocol appear less useful as a routine investigation. For example, tandem mass spectrometry of blood and/or bile did not reveal any deaths due to fatty acid oxidation





**Fig. 2.2** Causes of death in explained SUDI. Of explained deaths, the majority (60%) were due to an infective process, most commonly pneumonia (22%), whilst the commoner non-infective causes of death included congenital malformations (7%), and deaths due to accidental (6%) and non-accidental (10%) injuries (adapted from Weber et al. [59])



**Fig. 2.3** Component of the post-mortem examination which primarily determined the final cause of death: histological examination in 46% of explained SUDI, 17% of all SUDI, macroscopic examination in 30% of explained SUDI, 11% of all SUDI, microbiological investigations in 19% of explained SUDI, 7% of all SUDI and the clinical history/circumstances of death in 5% of explained SUDI, 2% of all SUDI. Toxicological analyses were performed in only selected cases and revealed the cause of death in only one infant due to accidental heroin poisoning (adapted from Weber et al. [59])

disorders in this series of infants aged 1 week to 1 year, although previous studies have reported such metabolic diseases as causes of death in this patient group. Combining the data from previous studies, deaths due to possible metabolic disorders represent only 0.3% of all SUDI deaths [1, 59–62] and in such cases, it is

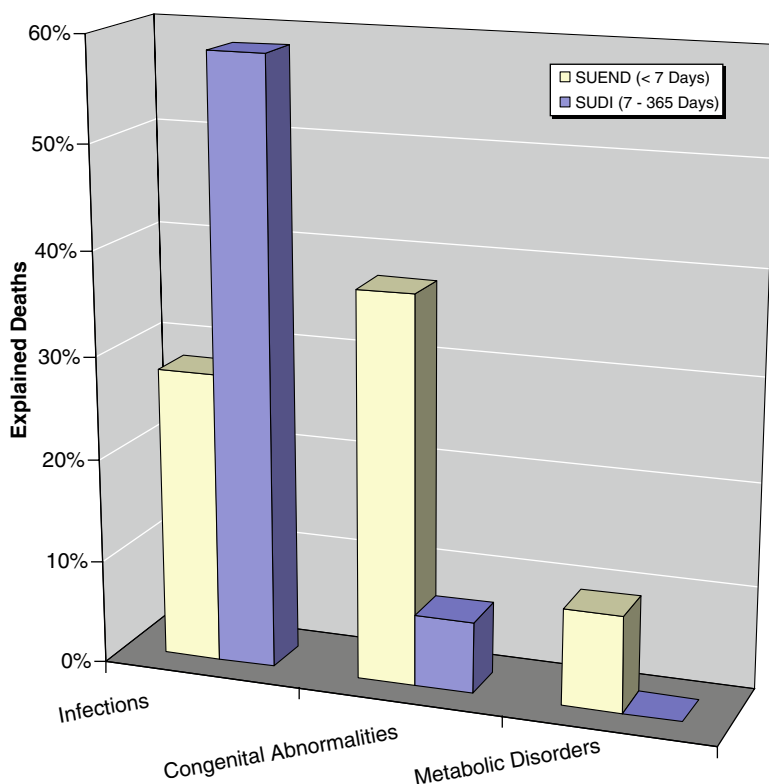
expected that there would be abnormal fat accumulation in liver, renal tubules and muscle, and hence histological screening with retention of additional samples may be a more cost efficient protocol rather than routine tandem mass spectrometric analysis. In addition, at present, post-mortem microbiology interpretation may be problematic in individual cases, being based on empirical guidelines only [43] (*vide infra*). Further studies may allow identification of the abnormal host immune response in such cases rather than attempting to isolate the organism responsible, which will allow separation of cases with incidental colonisation from cases with death due to an inflammatory response to infection.

## **Sudden Unexpected Early Neonatal Death**

Neonatal deaths occur in around 1 in 250 births, most being expected complications of prenatally or clinically detected congenital abnormalities, or complications of prematurity [63]. However, sudden unexpected neonatal deaths of otherwise clinically healthy infants in the first week of life, analogous to SUDI in older infants, may also occur; such deaths may be referred to as sudden unexpected early neonatal deaths (SUEND), although the clinical usefulness of separating SUEND from SUDI remains undetermined. However, in contrast to SUDI, in which around two-thirds of deaths remain unexplained after a full investigation, in a series of 55 SUEND cases, representing about 30% of early neonatal deaths undergoing autopsy, and 6% of all infant autopsies in that series, almost two-thirds (60%) were medically explained following post-mortem examination, with only one-third remaining unexplained, similar to SIDS in older infants [64]. Interestingly, 70% of cases who died during sleep were co-sleeping with parents, including almost all (90%) of the unexplained deaths that occurred during sleep. Explained deaths were due to previously undiagnosed congenital abnormalities (40%), mainly (>90%) structural congenital heart disease. In addition, there were three deaths (5%) from unsuspected metabolic disease, including two infants with medium chain acyl-CoA dehydrogenase deficiencies and one case of carnitine acylcarnitine translocase deficiency; 15% of deaths were due to clinically unsuspected infections, with no accidental or non-accidental injury-associated deaths in this age group. Therefore, a significantly greater proportion of SUEND were explained following post-mortem examination compared to SUDI cases, and a significantly greater proportion of these were due to congenital abnormalities and metabolic diseases, with less infection-related or traumatic deaths (Fig. 2.4).

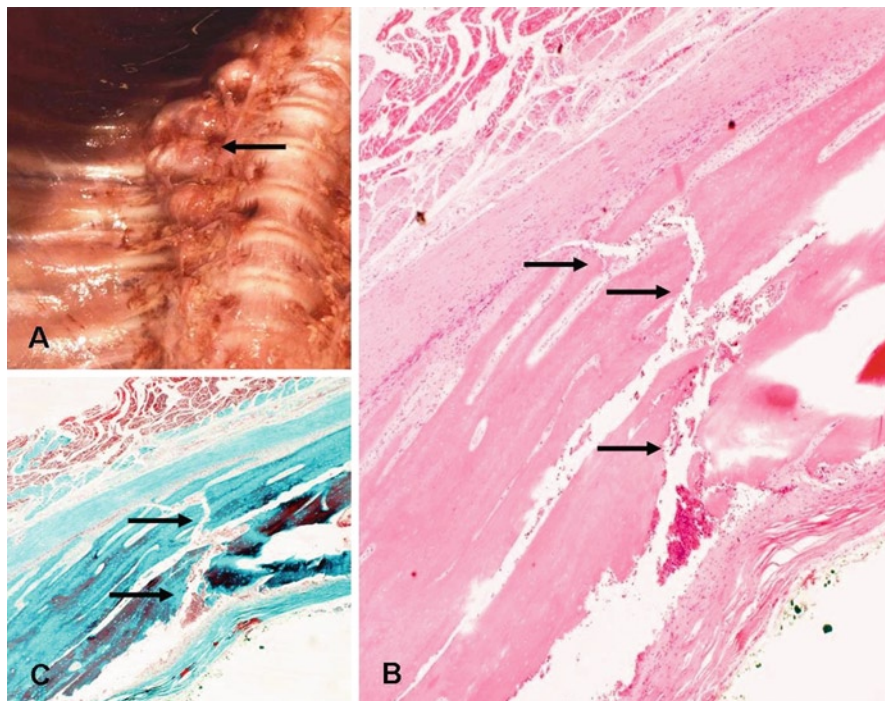
## **Interpretation of Rib Fractures in SUDI Autopsies**

Rib fractures are a well-recognised component of non-accidental injury (NAI) in infancy, usually being multiple, of varying ages and associated with other features of physical abuse [65]. The detection and confirmation of rib fractures is therefore



**Fig. 2.4** Compared to SUDI, there were significantly less SUEND deaths due to infections, with significantly more SUEND deaths due to congenital abnormalities and metabolic disease (adapted from Weber et al. [64])

a mandatory component of the SUDI post-mortem examination, including by radiological examination, by macroscopic rib inspection and by histological sampling of apparent fractures for confirmation and dating. Recent data from an autopsy series in which ribs were routinely examined by stripping of the parietal pleura and macroscopic inspection of individual ribs, preceded by routine post-mortem radiology reported by specialist paediatric radiologists with expertise in NAI, rib fractures were detected in 4% of all SUDI autopsies [66]. These included healing fractures in 15 infants (3% of all SUDI; 63% of those with rib fractures) and fresh fractures with no histological evidence of a surrounding tissue reaction in 9 infants (2% of all SUDI; 37% of those with rib fractures; Fig. 2.5). Of the 15 infants with healing fractures, 10 (67% of healing fractures) were associated with additional features suggestive of NAI. In contrast, of the nine infants with exclusive fresh rib fractures, seven (<2% of all SUDI; 29% of those with rib fractures; 78% of those with fresh rib fractures) demonstrated no other injuries and no additional features suspicious of NAI or major trauma, suggesting that these fractures were caused by



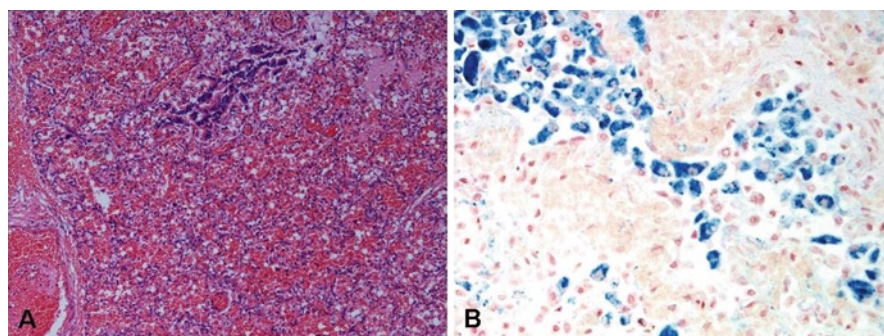
**Fig. 2.5** Rib fractures in SUDI. (a) Macroscopic appearances of healing rib fractures in an infant with suspected NAI, with posterior healing rib fractures showing prominent callus formation (arrow). (b) (H&E) and (c) (Masson Trichrome). Photomicrographs of fresh rib fractures, demonstrating the fracture line (arrows) associated with minor fresh haemorrhage only. There is no surrounding inflammatory reaction or periosteal reaction

resuscitation-associated trauma. These apparent resuscitation-related fresh rib fractures were multiple, all involving the fourth and fifth ribs, and almost exclusively limited to the third, fourth, fifth, and/or sixth ribs, and all were located anterolaterally, compared to predominantly posterior fractures in cases with other features of NAI. No resuscitation-related fractures involved the costochondral junction, these being found only in cases with other injuries suggestive of NAI. Interestingly, healing rib fractures were identified on routine post-mortem radiological skeletal survey in >90% of cases, whereas only 20% of fresh fractures were identified radiologically.

Pooled data from previous series suggest that about two-thirds of rib fractures are associated with NAI [67–71], with CPR-related fresh rib fractures occurring in about 1 in 300 episodes, using varying methods of ascertainment [72]. The frequency of detection of fresh fractures is greater in autopsy series in which specific stripping of the pleura and individual rib examination is carried out.

## Significance of Pulmonary Haemosiderin-Laden Macrophages in SUDI

Haemosiderin-laden macrophages (HLMs) in histological sections of lung represent evidence of previous pulmonary haemorrhage [73]. Pulmonary haemorrhage (Fig. 2.6a) has been reported in association with accidental and inflicted suffocation, although the sensitivity, specificity and quantification of intra-alveolar haemorrhage in this setting remain controversial [73–78]. It has been suggested that the presence of alveolar HLMs in infant lungs at post-mortem examination may be an indicator of NAI [79–81]. In a large series of almost 600 sudden infant deaths (comprising both SUEND and SUDI cases), 5% demonstrated alveolar HLMs on Perls' staining, often more prominent in the peripheral portions of the pulmonary lobule [82] (Fig. 2.6b). Around one-third with HLMs demonstrated additional features suggestive of NAI, about a third had a history of natural disease to explain their presence, and the remaining third were otherwise unexplained SUDI with no other significant post-mortem or clinical findings and no significant previous history or suspicious circumstances. Alveolar HLMs were almost ten times more frequent in those infant deaths associated with other features of NAI compared to those without other suspicious features, the effect remaining significant even when those with healing rib fractures were excluded. Thus, although the majority of cases with alveolar HLMs appear to be associated with previous natural disease, the presence of alveolar HLMs remains a potentially useful marker of NAI, although in isolation its interpretation is not diagnostic of previous asphyxia. Nevertheless, the presence of otherwise unexplained alveolar HLMs at autopsy should always prompt a careful exclusion of inflicted injury. In contrast, this association does not apply to interstitial HLMs (defined as HLMs limited to the interlobular septa, bronchovascular bundles and/or subpleural connective tissue), which are more prevalent in infants with increased birth weight and gestational age, and younger age at death, thought



**Fig. 2.6** Intra-alveolar haemorrhage and alveolar haemosiderin-laden macrophages (HLMs) in the lungs in SUDI. (a) (H&E). Fresh intra-alveolar haemorrhage. (b) (Perls' stain). Alveolar HLMs indicate previous haemorrhage; they can be detected within a few days after the haemorrhage occurred but may remain in the lungs for a long and variable period

to represent the consequence of pulmonary haemorrhage caused during labour, particularly in larger infants of greater gestational age, the HLMs then being gradually cleared during early infancy [83].

## Interpretation of Post-mortem Microbiology

Whilst post-mortem microbiological sampling is clearly important and may provide the cause of death in some cases of SUDI [1, 59, 62, 84–86], in practice, interpretation of findings is difficult because of potential issues of contamination, post-mortem translocation and overgrowth, as well as possible agonal spread [87] and distinguishing the clinical significance of positive findings from various sites. The role of infection contributing to the mechanism of death in some cases of otherwise unexplained SUDI is supported by the findings of a recent study in which routine post-mortem microbial isolates from cases of SUDI were classified as non-pathogens, group 1 pathogens (organisms usually associated with an identifiable focus of infection) and group 2 pathogens (organisms known to cause septicaemia without an obvious focus of infection: groups A and B beta-haemolytic streptococcus, pneumococcus, meningococcus, *Escherichia coli* and *S. aureus*) [43]. Of the 507 SUDI cases, including 379 unexplained SUDI, 72 non-infective explained SUDI and 56 explained SUDI deaths due to histologically confirmed bacterial infection (such as pneumonia or meningitis), including data on >2,000 samples with a median death to post-mortem interval of 3 days, around 30% were sterile, whilst the majority of cultures were positive for organisms. However, significantly more group 2 pathogens were isolated from the unexplained SUDI compared to the non-infective deaths; group 2 pathogens were detected in 50% of the unexplained SUDI group compared to only around 25% of the non-infective SUDI group. Specific organisms in this group most commonly detected included *S. aureus* and *E. coli*, predominantly from the lung. These data suggest that 10–35% of otherwise unexplained SUDI deaths in whom there is no histologically identifiable focus of infection at autopsy are related to infection with group 2 pathogens. However, interpretation in individual cases remains difficult, and discussion with a microbiologist is recommended in selected cases, particularly if there is no histological evidence of infection. Until further evidence becomes available, as a general rule, isolating the same pathogenic organism from multiple sample sites at post-mortem is likely to be more significant than isolating a pathogenic organism from a single culture site only; furthermore, it has been suggested that a pure growth or single isolate is more likely to be clinically significant than a mixed growth of organisms [87], although at present this is based on empirical grounds. The likelihood of clinical importance of a positive culture result of a recognised pathogen may be further modified by review of the clinical history, since symptoms and signs of a developing infection may have been present but unrecognised by carers prior to the death. Other markers of sepsis in life, such as white cell counts or CRP, which are not currently used in standard autopsy practice, may also prove to be helpful in this context, and may help to



change the likelihood of a positive culture result from “possible contributor” to “probable contributor” to the cause of death [88].

## **Role of Neuropathology in SUDI Autopsies**

Formal examination of the central nervous system is an integral part of the SUDI autopsy investigation, since in a small proportion of cases a definite cause of death can be identified, such as meningitis or congenital malformation [1, 59]. Furthermore, and perhaps more importantly, such examination is required for the exclusion of traumatic brain injury, such as cerebral oedema, diffuse axonal injury, and subdural or retinal haemorrhage [89]. However, controversy exists surrounding even the significance of these findings in this clinical setting [90, 91]. Furthermore, a large volume of literature reports on neuropathological findings in SUDI, much of which relates to subtle abnormalities particularly of the brainstem, which may be relevant to the underlying pathogenesis of SUDI [53–57]. These specific issues regarding formal detailed neuropathological examination are therefore beyond the scope of this review.

## **Role of Toxicology in Routine SUDI Autopsies**

The Kennedy protocol [13] does not make toxicological analysis mandatory in every case, and most centres in the UK would not routinely perform such investigations in otherwise non-suspicious deaths in whom there is no history of parental drug use [1, 59]. There is no doubt that toxicological analysis may reveal a cause of death in a small proportion of cases, ranging from less than 1 to 4% of sudden infant deaths [59, 86, 92, 93]; in one study of 117 SUDI, the finding of possible methadone toxicity had not been expected from the clinical history available to the pathologist prior to the post-mortem examination in three cases (3%) [93]. It is therefore possible that a small number of deaths due to accidental or intentional poisoning are missed if toxicology is not routinely performed, but its role in unselected SUDI cases currently remains undetermined.

## **Towards an Evidence-Based Protocol**

The optimal autopsy protocol remains empirical at present, but increasing evidence is accumulating to guide the development of modifications to this approach. Full autopsy with histological sampling and multiple site bacteriology is required in all cases. Post-mortem radiology and examination of ribs are also mandatory in every case. Issues regarding the extent of histological sampling, and from which organs,

remains uncertain and non-evidence based. The brain must be examined if no cause of death is identified, but the specific role of formal neuropathological examination as opposed to limited sampling for determining cause of death on behalf of HM Coroner remains unclear. Toxicological investigation clearly plays a role, but its usefulness in unselected SUDI cases remains undetermined, and, as outlined above, the interpretation of post-mortem microbiological cultures is also currently based on empirical principles. Future studies are required to address these issues in order to provide a true evidence base for the autopsy protocol in SUDI. Optimal pathological classification of these deaths, too, remains unclear, “unexplained SUDI” being most appropriate immediately post-autopsy if no cause is identified, with a case conference or HM Coroner decision on the final classification of death following a detailed and comprehensive review of the circumstances of death and to account for issues such as co-sleeping-associated deaths.

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