Infection: the neglected paradigm in SIDS research

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ABSTRACT
Despite decades of investigation and millions of dollars spent, the cause(s) of sudden infant death syndrome (SIDS) eludes researchers. It is timely therefore to reconsider the reasons for this failure and to explore how research might go forward with better prospects. This review assesses SIDS research in the context of clinicopathological and epidemiological features and determines that only infection attains congruence.

INTRODUCTION
Despite decades of investigation and millions of dollars spent, the cause(s) of sudden infant death syndrome (SIDS) eludes researchers. It is timely therefore to reconsider the reasons for this failure and to explore how research might go forward with better prospects.

SIDS is defined as the unexpected death of an infant <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.1 The ‘triple risk’ hypothesis accommodates multiple aetiologies (it proposed that SIDS occurs in infants with latent biological vulnerabilities, exposed to external threats during a critical period in development).2 It has served as a basis to tackle the problem. Mainstream research has been undertaken on grounds that generally fail to accommodate all aspects of the epidemiology (comprising the SIDS risk factors) (box 1) and clinicopathology of SIDS (box 2). Mainstream researchers have tended to settle on hypotheses that lack broad-based considerations.

What are the established facts in SIDS? These have been established through numerous epidemiological investigations and reports of the gross and microscopic pathological findings. To successfully investigate a disease of unknown causation, it is essential that all of these ‘facts’ are taken into consideration.

The list of epidemiological associations shows that infection is a key potential contender in the causation stakes. Male gender predominance, winter seasonality, a vulnerable host (prematurity, genetic predisposition through important inflammatory, innate and adaptive immune response polymorphisms), pre-natal and post-natal exposure to smoke, low socioeconomic status and so forth, all fit an infection model. Congruence between the increased risk of prone sleep position and infection is supported by the increased risk of putting down the infants to sleep on contaminated surfaces. SIDS cases are unusual in showing colonisation by coliforms in the respiratory tract17–19 and by toxigenic organisms such as Staphylococcus aureus in the gut.10 Respiratory tract colonisation by coliforms in SIDS carries an OR of 29 compared with healthy age-matched infants. Reasons for these colonisation features would seem to relate to prone sleep position enhancing ingestion/inhalation of bacteria on the sleeping surface especially because bacterially contaminated surfaces (sofas, previously used mattresses, parental bed,) are all risk factors for SIDS.5 14 20 21 Notably the risk of SIDS is increased by exposure to smoke while sleeping in the parental bed.13 Also of note, smoking mothers increase the risk of bacterial and/or viral colonisation in their infants.17 22

AUTOPSY FINDINGS
At autopsy, there may be frothy white or blood-stained secretions at the nares suggestive of pulmonary oedema.23 There is some evidence to indicate a febrile episode prior to death given that the core temperature is frequently elevated22 and clothing may be sweat-soaked.24

The bladder is usually empty.23 Agonal processes or anuria secondary to hypotensive shock as part of septic shock have been proposed.

Characteristic internal findings are exemplified by the triad of intrathoracic petechial haemorrhages involving the thymus, visceral pleura and epicardium. In most studies, ≥90% have the petechial triad. Notably the type and distribution of the petechiae differ significantly from those found in cases of asphyxia.25 26 Mainstream researchers attribute intrathoracic petechiae to changes in pulmonary pressure; however, this hypothesis does not stand up to scrutiny as argued in previous publications.27–29 Studies by Krous et al30–31 disproved an association between intrathoracic petechiae and prone position, indicating that hypothetical upper airway obstruction attributable to face-down position is not causally related to development of intrathoracic petechiae.

The lungs are congested and heavy23 indicating pulmonary oedema/early shock lung as may occur in septic shock. Cardiogenic causes of lung changes (eg, left ventricular failure, non-shock) would also fit.

Brain weight (and head circumference) is greater in SIDS cases than comparisons12–37 and is acknowledged by the National Institute of Child Health and Human Development (NICHD).38

Thymomegaly in SIDS has been the subject of considerable debate and has not yet been resolved satisfactorily.

The kidneys39 and heart40 are lighter than normal. These could also reflect intrauterine growth abnormalities incorporating biological vulnerability (as above).

The blood within the chambers of the heart is liquid/uncotted in almost every case.23
Box 1  Epidemiological associations/risk factors for sudden infant death syndrome (SIDS)

- Genetic predisposition (intrinsic) factors
  - Gender (and possible X-linked genetic mutations/copy number variations, etc)
  - Genetic control innate and adaptive immunity, inflammatory response
  - Genetic control of nitric oxide synthetase 1 (NOS1)
  - Genetic control of brainstem function
  - Genetic control of metabolic pathways, for example, flavin-monooxoxygenase 3, an enzyme metabolising nicotine
  - Genetic control of cardiac function
  - Ethnicity

- Extrinsic factors
  - Demographic factors
  - Low socioeconomic status
  - High birth order/previous live births

- Prenatal risks
  - Poor prenatal care
  - Maternal smoking/nicotine use
  - Inadequate prenatal care
  - Inadequate prenatal nutrition
  - Maternal misuse of heroin, cocaine and other drugs
  - Subsequent births less than 1 year apart
  - Alcohol use
  - Infant being overweight
  - Mother being overweight
  - Teen pregnancy (if the baby has a teen mother, it has a greater risk)
  - Mother single, divorced or separated
  - Maternal anaemia

- Post-natal risks
  - Seasonality
  - Viral respiratory or gastrointestinal symptoms in the days before death
  - Prematurity
  - Low birth weight
  - Exposure to tobacco smoke
  - Prone sleep position (lying on the abdomen)
  - Sleeping prone while intestinally colonised with Staphylococcus aureus
  - Not breastfeeding
  - Elevated or reduced room temperature
  - Excess bedding, clothing, soft sleep surface and stuffed animals
  - Co-sleeping with parents or other siblings
  - Sofa-sleeping
  - Sleeping on a used mattress
  - Sleeping in parental bed
  - Infant’s age (incidence rises from zero at birth, is highest from 2 to 4 months and declines towards zero at 1 year)
  - Prematurity (increases risk of SIDS death by about four times)
  - Probable anaemia (haemoglobin cannot be measured postmortem)
  - Early cord clamping (possibly causing anaemia)
  - Recent visit to general practitioner/outpatient clinic
  - No or late immunisation
  - Day care attendance
  - Night-time death

Box 2  Pathological findings

- Raised core (rectal) temperature
- Frothy exudate at nares
- Intrathoracic petechiae involving thymus, visceral pleural and epicardium
- Organ weight changes:
  - Heavy brain, thymus
  - Light heart and kidneys
  - Heavy congested lungs
- Mild acute inflammatory changes in airways, lungs and myocardium
- Liquid/unclotted blood in chambers of heart
- Empty bladder
- Normally sterile site yielding a bacterial pathogen
- Proteomic and immunohistochemical evidence of infection (acylcarnitine, CD68, intercellular adhesion molecule-1, etc)

HISTOPATHOLOGY
Histopathology shows mild inflammatory changes within the lungs (reflecting recent viral infection) in a large proportion of cases. The brainstem may show subtle changes in a minority of cases (discussed below). The intestine may show inflammatory or other changes; pathologists often report autolytic change. Reports of cardiomyocyte and diaphragm myocyte changes have been demonstrated but do not seem to have been corroborated. Evidence of a systemic inflammatory event is present in some cases of SIDS (discussed below).

CLINICAL FINDINGS
Poets has provided several important clues to understanding the aetiopathogenesis of SIDS. Babies whose moment of death was captured on memory monitors showed a progressive decrease in heart rate, which developed over minutes or hours. A total of 14 recordings are published. Witnessed cases have been reported.

Poets concluded that none of the recordings showed evidence of the occurrence of prolonged central apnoea as the primary cause of death. The exact cause(s) of the bradycardia could not be determined from the recordings, but there is evidence from similar recordings that have been obtained during apparent life-threatening events and which included data on oxygenation that showed progressive heart rate slowing was probably due to hypoxic cardiac depression. In the monitored SIDS cases, breathing continued in the form of gasping and followed cardiac standstill. Hypoxaemia as part of the lethal episode in SIDS seems to be well accepted; however, the cause of hypoxaemia deserves reconsideration. One important cause seemingly overlooked by mainstream researchers is infection and sepsis.

Inflammatory markers in SIDS
C reactive protein is not consistently detected or elevated. In her review, Blood-Siegfried assembled convincing autopsy and other evidence of infection and inflammatory responses in SIDS. Similarly, Blackwell et al summarised the evidence in terms of risk factors and specific tissue and serum findings of inflammatory markers. Both reviews confirm strong links between infection/inflammation and SIDS. Some of the evidence is contained in studies of genes involved in inflammatory...
responses. Examples include a tumour necrosis factor-α polymorphism responsible for high cytokine production and an interleukin (IL)-1α polymorphism in parents of SIDS babies associated with an exaggerated response to toxic shock syndrome toxin. Others include an IL-6 polymorphism (IL-6-174G/C), associated with specific ethnic background of SIDS cases and a number of IL-10 polymorphisms associated with population-specific variations in polymorphisms and indicate other risk factors must also play a role.

MICROBIOLOGY
As mentioned above unusual colonisation by coliforms and toxigenic organisms is a feature of SIDS and goes some way to explain the risk factor of prone sleep position particularly in relation to the heightened risk associated with contaminated sleeping surfaces. At autopsy normally sterile sites (heart chamber blood, spleen, cerebrospinal fluid) may contain a bacterial pathogen (e.g., S. aureus, Escherichia coli, other coliforms) in about one-fifth of cases. This could represent a footprint of a lethal bacteraemic episode. Coliforms and S. aureus are isolated from the lungs and airways more frequently from SIDS cases than non-SIDS deaths. Evidence of viral infection involving the airways, lungs, heart and the small intestine is relatively common. As mentioned above, maternal smoking promotes viral colonisation in their infants.

New technology including proteomics is helping in identifying the role of infection in SIDS. The Great Ormond Street Hospital group, which used tandem mass spectrometry, could not distinguish SIDS from autopsy-proven infection-related deaths on the basis of acylcarnitine and other related compounds associated with infection, which strongly indicated that infection was temporally related to SIDS deaths and supports the infection hypothesis of SIDS aetiopathogenesis.

THE MICROBIOME AND SIDS
Early studies show differences between the gut microbiome of SIDS babies compared with healthy babies. The study by Highet and Goldwater goes some way to explain the risk factor of prone sleep position with an infinitely high OR for the occurrence of gut colonisation with S. aureus and prone position of infants when found. S. aureus (frequently enterotoxigenic) seems to more commonly colonise babies’ intestines in the first year of life while E. coli colonisation is on the decline. Extraintestinal E. coli are frequently found in SIDS babies and are isolated from normally sterile sites and often from the airways and lungs in SIDS babies and rarely in non-SIDS cases. α-Haemolysin (HlyA)-producing uropathogenic E coli strains causing urinary tract and other extraintestinal infections are found more frequently in SIDS infants compared with healthy babies or non-SIDS deaths and serotypes O1:H-, O1:H5, O2: H1, O4:H5, O6:H1, O25:H1 and O75:H5 are over-represented in SIDS. Bäcker et al. found that α-HlyA of E. coli triggers intestinal inflammation in mouse models of inflammatory bowel disease by impairing the intestinal barrier and thereby intensifying antigen uptake. Such a mechanism could operate in SIDS wherein an inflamed gut mucosa could promote microbial translocation into the bloodstream and cause overwhelming sepsis. New information showing an otherwise previously unknown microbiome of the airways and lungs could also involve predisposition to abnormal inflammatory responses.

Metagenomics reveals additional data indicating the importance of gut microbiome dysbiosis in relation to development of disease such as obesity, type 1 diabetes, colitis and metabolic syndrome. A preliminary metagenomics study by Leong et al. has demonstrated a significant association between Aerobacteriaceae and SIDS but previously shown associations between S. aureus, E. coli and Clostridia was not corroborated in this small sample (29 SIDS; 21 controls).

CLOTTING SYSTEM IN SIDS
The blood within the chambers of the heart is liquid/unclotted and remains unexplained; however, raised fibrin degradation products (FDPs) are characteristic of SIDS. Evidence of disseminated intravascular coagulopathy (DIC) is usually not found. While the inthoracic petechiae haemorrhages could represent a distinct vasculopathy, linking this to raised FDPs has not yet been established. Systemic infection is recognised as being linked to elevated FDPs without the development of DIC. The question remains as to the underlying reasons for raised FDPs in SIDS. Abnormally increased FDPs are an indication of increased fibrinolytic activity and are not specific to DIC.

CRITIQUE OF MAINSTREAM APPROACH
Mainstream researchers have tended to focus on a single pathological finding and have developed hypotheses centred on this while tending to ignore the epidemiology/risk factors or the other clinico pathological findings. Examples include intrathoracic petechiae as the basis for an asphyxial event. Evidence to support this idea is either lacking or raises serious questions; for instance, why is the distribution and number of petechiae affected by the age, ethnicity, parity, exposure to cigarette smoke and the sleep position? Or why infants placed prone show a reduced frequency of pleural petechiae?

Another major area of mainstream research focuses on brainstem, limbic forebrain and hippocampus and possible central homeostatic control. Isolated pathological findings (such as hypoplasia of the arcuate nucleus (respiratory chemosensitive zone of the ventral medulla) and gliosis of cerebral white matter) occur only in a minority of cases. This focus, limited to a single anatomical site, ignoring overall morbid pathology or epidemiological associations leaves the hypothesis wanting in many respects. Similarly wanting are research paths taken based on a single finding such as prone position found, head covered by bedding, sleeping and dying in the parental bed (overlying). Other researches have centred on the heart, given that adult sudden deaths have been attributed to cardiac dysrhythmia such as QT interval genetic pathology and other causes of channelopathy or brainstem dysfunctional control. Genetically diagnosed channelopathies are found in a minority of SIDS cases. The finding does not necessarily mean the inherited channelopathy actually caused the deaths. Nor does anatomical abnormality of brainstem neuronal nuclei necessarily relate to causation of death, given that similar findings are observed in brainstems of non-SUDI deaths, although in a smaller proportion. These hypotheses are speculative and lethality is not necessarily established in relation to the purported underlying problem nor have animal models provided clear answers.

A major failing of mainstream investigations is the rarity of inclusion of general autopsy findings in their publications that could otherwise provide useful information. We are not privy to the intrathoracic findings or nature of the heart blood (clotted/unclotted) or organ weights of cases reported, for example, in relation to hypotheses based on brainstem or cardiac aetiologies. If pertinent information were published, it could become clearer that purported cardiac channelopathies were associated with a specific pathological picture, for example, absent intrathoracic
petechiae that could help explain the <10% of SIDS cases lacking the typical pathological findings (triad of petechiae, liquid cardiac blood, large brain, heavy wet lungs, etc).

POSSIBLE LETHAL PROCESS

Male gender is a risk factor for almost all infections85 (pertussis being the exception). Akin to infection, X-linked genetic susceptibility would apply in the instance of SIDS.85 In consideration of a lethal process that would fit with the epidemiology and clinicopathological findings there would appear to be only one—that is bacterial infection and overwhelming sepsis/septic shock. This is not a new proposal; Morris et al86 provided the common bacterial toxin hypothesis encompassing sepsis and/or toxic shock. Other groups accept and explore this approach.87

These authors have shown that toxigenic organisms notably ones normally considered non-pathogenic commensals may well have an important role in SIDS pathogenesis. Bacterial infection accompanied by viral infection may exacerbate the effects of bacterial infection.94 Similarly, dual bacterial infection produces a lethal synergy.95 Bacterial infection and septic shock is often difficult to diagnose in life as it is at autopsy.95 In a vulnerable host, death from sepsis can be rapid and can be missed at autopsy. Rapid-onset sepsis and death may not leave the hallmark of infection and there may be no features of sepsis apparent at autopsy except for bacteria in normally sterile sites in some cases. CD68 cells and other markers of infection are not consistently found in the lungs of SIDS cases96 and may reflect the rapid nature of the septic process before conscription of sufficient immune cells to be left as a marker. The immature immune system of neonates who have died of confirmed sepsis show extremely variable innate and adaptive immune responses. Indeed many infants have no evidence of CD68 or CD54 cells in their lungs or other tissues. Intercellular adhesion molecule-1 (ICAM-1, CD54) is a cell surface protein that is expressed at very low levels on pulmonary endothelium, lymphocytes and macrophages. Expression of ICAM-1 is upregulated on stimulation by inflammatory mediators such as cyto-ICAM-1 that mediate inflammatory responses by adhesion of leucocytes to activated endothelium and subsequent leucocyte translocation through the pulmonary endothelial layer.96

Doberentz et al97 examined CD45RO, CD68 and leucocyte common antigen-positive cells in pulmonary tissue and the cell adhesion molecules E-selectin, P-selection and ICAM-1 and found no difference between SIDS and non-SIDS cases. The lack of a consistent finding reflects the situation of suspected fatal sepsis wherein the microscopic autopsy lung findings may be minimal, non-specific or unconvincing. Confounding our understanding is the lack of detailed published pathological information with respect to the existence or otherwise of intrathoracic petechiae and liquid heart blood in cases of fatal neonatal sepsis.

CONCLUSION

Mainstream researchers propose multiple causes of SIDS to accommodate the several organ system-based lines of research (box 3). If multiple causes were involved, then it would be reasonable to expect a variety of pathological findings. This demonstrably is not the case. There is a fixed pattern to the vast majority of cases. The crux of the argument against broad poly-causality of SIDS is the consistent pathological picture (usually in more than 90% of cases). Given this consistency of pathological findings and their congruency with the SIDS risk factors and giving due acknowledgement to Occam, it is logical to hypothesise a ‘single’ causal mechanism for those 90%. As indicated above, deaths from possible causes which form only a tiny minority of SIDS cases (eg, channelopathies) may not exhibit the classical pathological of SIDS and therefore provide an explanation for ‘different’ pathological findings such as the absence of intrathoracic petechiae or the finding of normal organ weights. It is therefore essential that the overall pathological findings of suspected channelopathy or brainstem pathology cases are published. Inclusion of the epidemiological features is also desirable.

In moving forward, SIDS researchers should be asking the following questions: (1) Does my hypothesis take into account the key pathological findings in SIDS? (2) Is my hypothesis congruent with the key epidemiological risk factors? (3) Does the hypothesis link questions (1) and (2)? This review has shown that infection meets these questions appropriately and researchers in this area deserve acknowledgement and funding support. There remain gaps in our knowledge with regard to the infection model, but it is clear that other lines of research are not making the grade. How the microbiome shapes the immune system in infancy98 could be the key in the SIDS story especially in relation to host pathogen recognition and vulnerability. It is hoped that in future we will see support and action in line with a more enlightened approach to solving the tragic enigma of SIDS.

Box 3 Sudden infant death syndrome research approaches

- Brainstem control of respiratory function
- Brainstem control of cardiac function
- Respiratory obstruction/unintentional asphyxia
- Cardiac channelopathy
- Common bacterial toxins/sepsis/toxaemia
- Shock including anaphylaxis
- Thermal stress
- Diaphragmatic failure
- CO2 rebreathing, CO2 poisoning
- Helicobacter pylori infection
- Respiratory infection
- Pneumocystis jiroveci (carinii) infection
- Inborn errors of metabolism
- Genomic load of deleterious mutations
- Physiological anaemia (from early cord clamping)
- Fatal anoxic encephalopathy associated with respiratory tract infection (RTI) (Mage and Donner85)
- Toxic gases from mattress
- Overlaying
- Abuse

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