Cytokine responses and sudden infant death syndrome: genetic, developmental, and environmental risk factors

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Abstract: Despite the success of the campaigns to reduce the risk of sudden infant death syndrome (SIDS), it still remains the major cause of postneonatal mortality. The incidence of SIDS is higher among ethnic groups in which there are also high incidences of serious infectious diseases. The risk factors for SIDS parallel those for susceptibility to infection, and recent data have provided evidence to support the mathematical model of the common bacterial toxin hypothesis. One current hypothesis for the etiology of SIDS is that the deaths are a result of overwhelming proinflammatory responses to bacterial toxins; as in inflammatory responses to sepsis, cytokines, induced by bacterial toxins, cause physiological changes leading to death. The genetic, developmental, and environmental risk factors for SIDS are reviewed in relation to colonization by potentially harmful bacteria and the inflammatory responses induced in the nonimmune infant to microorganisms or their products. *J. Leukoc. Biol.* 78: 1242–1254; 2005.

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INTRODUCTION

Despite successful public health campaigns to reduce the risk factors for sudden infant death syndrome (SIDS), it is still the major cause of death between 1 month and 1 year of age among infants in industrialized countries. SIDS is a diagnosis of exclusion. The original definition was ". . . the sudden death of any 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" [1]. The definition was revised in 1989 to "the sudden death of an infant under one year of age which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history" [2, 3].

The major risk factors for SIDS parallel those for serious bacterial infections in infants and young children, particularly infections of the respiratory tract (**Table 1**). These include genetic, developmental, and environmental factors, which could contribute to enhanced colonization of infants by potentially pathogenic microorganisms or severity of inflammatory responses to infection. The genetic and developmental factors are not modifiable; therefore, the campaigns to reduce the risks of SIDS have concentrated on environmental factors such as sleeping position, exposure to cigarette smoke, and prevention of overheating.

EVIDENCE OF INFLAMMATORY RESPONSES IN SIDS

Two recent reviews summarized the evidence for inflammatory responses in SIDS [27, 28]. Inflammatory changes (**Table 2**), particularly in the respiratory tract, are common findings in SIDS and probably reflect recent infections, which have been noted in the 2 weeks prior to death for over 40% of SIDS infants [41, 42]. Myonecrosis of the myocardium and the diaphragm in SIDS babies, similar to lesions described in cases of shock, have been reported [43, 44]. Perturbation of the clotting system [40] has been suggested to be responsible for the high proportion of SIDS infants in whom blood remains liquid. This might be associated with increased numbers of mast cells [29] and evidence of mast cell degranulation [30, 32] noted for many SIDS infants. Release of heparin might account for liquid blood, and release of preformed tumor necrosis factor α (TNF-α) or other vasoactive compounds could contribute to anaphylactic-like responses. Identification of pyrogenic staphylococcal toxins in brain tissue has been proposed as one explanation for the brain edema noted in many SIDS infants [28]. Evidence of immune/inflammatory activation in tissues and secretions of SIDS infants has been reported [27, 28, 31, 34].

The most direct evidence for cytokine involvement comes from studies in which half of the SIDS infants investigated had IL-6 concentrations in their cerebrospinal fluid (CSF) equiva-

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TABLE 1. Risk Factors for SIDS, Which Parallel Risk Factors for Susceptibility of Infants to Infection

Risks	Reference
Genetic	
Ethnicity	[4–12]
Male gender	[13–15]
Developmental	
Night-time deaths	[16, 17]
Peak age range 2–4 months	[14]
Environmental	
Prone sleeping	[13, 14, 18]
Cigarette smoke exposure	[13, 14, 16]
Overheating	[19]
Mild respiratory infections	[14, 19, 20]
Lack of breastfeeding	[21]
Poor socioeconomic conditions	[13, 14, 22]
No or late immunization	[23, 24]
Air pollution	[25]
Used cot mattress	[13, 26]

lent to those found for infants dying from infectious diseases such as meningitis or septicaemia [36]. Other cytokines implicated in experimental studies of SIDS include IL-1β, which has been shown in animal models to interact with nicotine and interfere with autoresuscitation [45].

INFECTION AND SIDS—VIRUSES OR BACTERIA?

The age distribution of SIDS is the most consistent feature of the condition. The risk of SIDS increases rapidly to a peak at 2–4 months of age and then falls. These deaths are less common after 6 months. The risk of SIDS is approximately reciprocal to infant serum immunoglobulin (IgG) levels. IgG protects against extracellular bacteria and neutralizes bacterial toxins. These observations were the basis for the common bacterial toxin hypothesis of SIDS, a mathematical model that closely predicts the characteristic age distribution but only if the microorganisms responsible are common. According to the model, 50% of infants must meet the organism in any 50-day period. This implies common bacteria of the normal microbial flora rather than less common pathogenic viruses [46–48].

By definition, invasive bacterial infections are explainable causes of death and therefore, not involved in SIDS. Although virus infection might be an important cofactor in the series of events leading to death, there is little evidence that SIDS is a result of an unrecognized viral disease [49]. Toxigenic bacteria and/or their toxins have been identified in SIDS infants in studies from several different countries (**Table 3**). Many bacterial species express molecules that act as superantigens. The cytokines they induce, if not moderated, can cause tissue damage or death. They are responsible for the pathology of septic and toxic shock [82]. It has been suggested that SIDS is a result of rapid, uncontrolled release of inflammatory mediators in response to infectious agents or their toxins [83]. A survey of SIDS infants found little or negligible levels of antibodies to bacterial toxins [37, 38]. In the absence of protective antitoxins, the inflammatory mediators induced by these toxins could produce significant changes in each of the physiological mechanisms proposed to explain these deaths—hypoxia, poor arousal, hypoglycaemia, vascular shock, cardiac arrythmias, hyperthermia, and anaphylaxis [84, 85].

S. aureus best fits the predictions of the common bacterial toxin hypothesis. More than 50% of normal infants are colonized by *S. aureus* during the period in which SIDS is most prevalent [86, 87], and over 60% of these isolates from healthy children produced one or more pyrogenic staphylococcal toxins [88]. Although *S. aureus* was isolated from 56% of healthy infants 3 months of age or younger, 86% of SIDS infants in the same age range had these bacteria in the respiratory tract [87].

Staphylococcal toxins can kill healthy adults or older children [89, 90]. Staphylococcal enterotoxin A (SEA), B (SEB), C (SEC), or the toxic shock syndrome toxin (TSST) were identified in the tissues from over 50% of 105 SIDS cases from five countries (**Table 4**) [52, 85]. Toxins produced by staphylococci isolated from SIDS infants varied by geographic areas. Isolates from Scottish infants predominantly produced SEB and SEC. Isolates from SIDS infants in Hungary predominantly produced SEA, and SEC was produced by only one isolate obtained from a healthy child [53]. TSST was identified in tissues of SIDS infants from Australia [52].

TABLE 2. Inflammatory or Immune Responses Identified in SIDS Infants

System	Response	Reference
Respiratory tract	Peribronchial inflammatory infiltrates	[29,30]
	Increased IgM cells in trachea	[31]
	Mast cell degranulation	[32,33]
Digestive tract	Increased IgA cells in duodenum	[31]
	Increased salivary IgA	[34]
Nervous system	Interferon-α (IFN-α) in brain	[35]
	Increased levels of IL-6 in spinal fluid	[36]
Blood	Decreased IgG to bacterial toxins	[37,38]
	Increased IgM to core endotoxin	[38]
	Increased levels of mast cell tryptase	[33]
	Increased levels of mannan-binding lectin	[39]
	Cross-linked fibrin degradation products	[40]

IgM, Immunoglobulin M; IL-6, interleukin-6.

TABLE 3. Toxigenic Bacteria and Their Toxins Implicated in Sudden Death in Infancy

Species	Toxin	Superantigen	Reference
Staphylococcus aureus	Enterotoxins, TSST	yes	[50–53]
Bordetella pertussis	Pertussis toxin,	no	[54–58]
	endotoxin	yes	
Haemophilus influenzae	Endotoxin	yes	[59, 60]
Clostridium perfringens	Enterotoxin A	yes	[61, 62]
Clostridium botulinum	Botulism toxin	no	[63–65]
Streptococcus pyogenes	Pyrogenic toxins A & B	yes	[59]
Escherichia coli	Enterotoxins, verotoxins,	?	[66–72]
	curlin	yes	[73]
Streptococcus mitis	?	yes	[74]
Helicobacter pylori	Endotoxin, vacuolating toxin, urease	yes	[75–79]
Pneumocystis carinii	?	?	[80]
Pneumocystis jirovecii	?	?	[81]

LTSST, Toxic shock syndrome toxin; ?, toxin/antigen unknown.

A significant number of pathologists have dismissed microbiological findings in SIDS cases as post mortem artifacts, growth of organisms that occurred after death despite storage of the body in the cold prior to examination. A recent review of post mortem bacteriology indicates that few of the positive bacteriological findings are a result of artifact [91]. The criticism of post mortem artifact is not valid in relation to the staphylococcal toxins. They are produced only between 37°C and 40°C [92], conditions that will not be met after the child has died.

A second common bacterial toxin is endotoxin of Gram-negative bacteria. These organisms are isolated frequently from the upper respiratory tract of infants who died of SIDS [19, 30], and they are also found in significant numbers of older infants sleeping in the prone position [86]. Measurement of endotoxin in blood or tissues is controversial, even among live subjects [93]; however, in carefully designed animal studies, endotoxin levels in blood and a range of tissues were higher in rats injected with endotoxin immediately before death compared with control animals. The results were stable up to 4 days after death [94].

There were no significant differences in endotoxin levels in a study of blood and tissue samples of SIDS infants and controls; however, blood endotoxin levels were higher in SIDS infants in whom there was histological evidence of mild to moderate inflammation [95]. Experimental studies indicate that risk factors such as virus infection or presence of other bacterial toxins can potentiate the effects of endotoxin [96, 97].

TABLE 4. Detection of Pyrogenic Staphylococcal Toxins in SIDS Infants [52, 85]

Group tested	Toxin detected (no.)	%
French	7/13	55
German	13/20	65
Hungarian	13/23	57
Scottish	10/19	53
Australian	16/30	53*
Australian controls	3/19	16

* $P < 0.02$.

ANALYSIS OF THE RISK FACTORS FOR SIDS IN RELATION TO SUSCEPTIBILITY TO INFECTION

In relation to infection and inflammation, the risk factors identified in epidemiological studies of SIDS appear to have biological plausibility, and the effect of the risk factors can be tested in model systems. The recognized risk factors could affect three stages in the infectious process: frequency or density of colonization by the toxigenic species implicated in SIDS; induction of temperature-sensitive toxins; and modulation of the inflammatory responses to minor infection or toxins. The effects of the risk factors on each stage will be summarized briefly.

STAGE 1. BACTERIAL COLONIZATION

Density of colonization of mucosal surfaces plays an important role in development of disease [98]. There are genetic, developmental, and environmental factors that enhance acquisition of potential pathogens from the environment.

Genetic risk factors

Ethnic group

Children in some Indigenous groups are colonized earlier and more heavily by respiratory pathogens than children of European origin [99, 100]. The basis for this is not known but might reflect differences in expression of human cell surface antigens, which act as receptors for microorganisms [101], or environmental factors such as exposure to cigarette smoke or closer physical interactions with older siblings or other family members.

Gender

Male infants sleeping prone, with or without infection, had significantly higher counts of Gram-positive cocci (including *S. aureus*) compared with females [86].

Developmental risk factors

Age range

During the 2- to 4-month age range, 80–90% of infants express the Lewis[a] antigen, and it was identified in respiratory secretions of 71% of SIDS infants examined in one study [102]. This antigen is one of the epithelial cell receptors for three species of bacteria implicated in SIDS: *S. aureus* [102–104]; *B. pertussis* [105]; and *C. perfringens* [106]. By 18–24 months, the antigen is usually found on red cells of 20–25% of children, a proportion similar to that observed in adults [107]. The decline in expression of Lewis[a] parallels the decrease in frequency of isolation of *S. aureus* from healthy infants [102].

Environmental risk factors

Prone sleeping position

Prone sleeping is a major risk factor for SIDS and implementation of "back to sleep" campaigns has contributed greatly to the worldwide reduction of these deaths. The prone position results in increased numbers of bacteria and an increase in the variety of species in nasal secretions of infants with respiratory virus infections. Increases in bacterial colonization might also be a result of decreased swallowing in the prone compared with the supine position. This is thought to contribute to the higher incidence of otitis media in infants who sleep prone compared with those who sleep in the supine position [108]. The composition of the nasal flora of the infants sleeping prone resembled that identified in the upper respiratory tract of SIDS infants but was reduced in numbers later in the day when the infant had been upright [86].

Exposure to cigarette smoke

"Passive" smoking implies a lower level of exposure to toxic components of cigarette smoke; however, some infants have levels of cotinine in their body fluids equivalent to those found in active smokers [109].

Smokers are more frequently colonized by staphylococci [110]. In experimental models, buccal epithelial cells (BEC) from smokers bound significantly more *S. aureus, B. pertussis*, and several Gram-negative bacteria [67]. BEC treated with water-soluble extracts of cigarette smoke showed that increasing tar content was associated with increased binding of staphylococci [111, 112], and the "sticky" effects of the extracts were present at dilutions as great as one in 300 [111].

Mild upper-respiratory tract infection

As noted above, inflammatory changes in the respiratory tract of SIDS infants are thought to reflect recent infections [113]. Medical records for 31 SIDS deaths in a Canadian Aboriginal population indicated the majority had symptoms of colds, virus infections, or breathing difficulties [42].

In an in vitro model using a human epithelial cell line, infection of the cells with respiratory syncytial virus (RSV; types A or B), influenza A, or influenza B significantly enhanced binding of *S. aureus* [102], *B. pertussis* [105], and a variety of other Gram-positive and Gram-negative species [114–116]. The changes in cell surface antigens, which can act as receptors for some bacterial species, could contribute to the increased binding observed [115, 116].

Breastfeeding

In vitro experiments have demonstrated that glycoconjugates such as the Lewis[a] and Lewis[b] antigens in human milk significantly reduce binding of *C. perfringens* and *S. aureus* to epithelial cells. Breast milk contains IgA, which can aggregate bacteria, making them easier to expel in mucus. It also contains antibodies specific for some adhesins involved in binding to epithelial cells [104, 106].

STAGE 2. INDUCTION OF TEMPERATURE-SENSITIVE TOXINS

Environmental risk factors

Prone sleeping position

The pyrogenic staphylococcal toxins are produced only in the temperature range 37–40°C. The temperature of the nasopharynx is usually below 37°C [117]. The nasal temperature in the prone, but not the upright position, was demonstrated to reach 37°C in five of 30 (16.7%) children who had no evidence of respiratory tract infection [118].

Overheating

Other risk factors that could increase the temperature to the permissive range in which the toxins can be induced include viral infection, blockage of nostrils with secretions during respiratory infections, and covering the face with bedding or clothing.

STAGE 3. RISK FACTORS AFFECTING INDUCTION OR CONTROL OF INFLAMMATION

Factors that enhance proinflammatory responses include: interactions between respiratory virus infections and bacterial toxins; interactions between different bacterial toxins; interactions between bacterial toxins and products of cigarette smoke; hyperthermia; and single nucleotide polymorphisms (SNP) of pro- and anti-inflammatory cytokine genes. The genetic background is being investigated at present in relation to differences in the incidence of SIDS noted among different ethnic groups (**Table 5**). Interactions between genetic and environmental factors are also assessed in relation to cytokine responses.

Enhancement of inflammatory responses

The major factors that have been found to enhance proinflammatory responses are environmental and genetic.

Environmental risk factors

Respiratory viral infections

In model systems, induction of proinflammatory cytokines, which contribute to severity of the host's responses to infectious agents or their products, can be enhanced greatly by coexisting virus infection [96, 97, 119–121]. Priming with an

TABLE 5. Variation in the Incidence of SIDS among Ethnic Groups within Countries before the "Reduce the Risks" Campaigns

Country	Ethnic group	SIDS/1000 live births	Ref.
Australia	Aboriginal	6.1	[4, 11]
	Non-Aboriginal	1.7	
United Kingdom	European	1.7	[5]
	Bangladeshi	0.3	
United States	Total population	2	[6, 7, 10]
	Oriental	0.3	
	African American	5.0	
	Native American	5.9	
	Alaskan Natives	6.3	
New Zealand	Maori	7.4	[8]
	Non-Maori	3.6	

asymptomatic virus infection can significantly reduce the concentration of bacterial toxins needed to induce death [97, 121].

Animal models have demonstrated that virus infection can change the cytokine response pattern following administration of sublethal doses of endotoxin, which results in dysregulation of the inflammatory responses. Morbidity and mortality were thought to be related to shock-like effects consistent with inflammatory cytokine responses and production of reactive nitrogen species. Usually, endotoxin induces a regulated series of events which result in a protective inflammatory response. In healthy human volunteers, serum levels of TNF-α peak at 1 h after endotoxin administration; this is followed closely by IL-1β, then IL-6 at 3 h, and IL-10 at 5 h [122]. Alterations in the kinetics of these events can induce an exaggerated response often seen in septic shock in which proinflammatory cytokines (TNF-α, IL-1β, IL-6, and IFN-γ) trigger a cascade of events leading to edema, systemic collapse, decreased blood volume, disseminated intravascular coagulation, organ failure, and death [123].

Combinations of bacterial toxins

Some of the toxigenic species identified in SIDS have been tested in combination with in vitro models to demonstrate additive or synergistic effects between the toxins [124].

Cigarette smoke

In an animal model, nicotine significantly enhanced the lethal effect of bacterial toxins [125]. Cotinine, a metabolite of nicotine, enhanced production of some inflammatory mediators from human monocytes. In the same model system, a water-soluble cigarette smoke extract enhanced TNF-α responses of human monocytes infected with RSV and enhanced nitric oxide (NO) production from monocytes exposed to TSST [126]. Mononuclear cells from smokers showed increased production of proinflammatory cytokines IL-6, IL-1β, and TNF-α. They also had strong proliferative responses to mitogens compared with nonsmokers [127]. Smokers had lower baseline levels of the anti-inflammatory cytokine IL-10 and lower levels of IL-10 in response to stimulation with TSST or endotoxin [85]. The relevance of findings for smokers for the health of infants or children is supported by the findings of Daly and colleagues [109], who reported that some infants have levels of cotinine similar to those found in adults.

Hyperthermia

The physiological effect of hyperthermia in relation to SIDS has been reported to be particularly significant in relation to infection [19]. Hyperthermia significantly increased production of IL-6 but not IL-1β in infant rats. In response to muramyl dipeptide (MDP), IL-1β was increased significantly but not IL-6. MDP, in combination with hyperthermia, significantly increased mortality of the animals [128]. These results suggest one possible mechanism underlying the protective effect of keeping infants cool, a recommendation of the Reduce the Risks campaigns.

Genetic risk factors

Ethnicity

Well before the campaigns to reduce the risk factors associated with SIDS, the incidence of SIDS among Indigenous groups was higher than those reported for other ethnic groups in the same country. Other groups such as Asian families in the United Sates or Britain had significantly lower incidences of SIDS compared with Caucasian families (Table 5). In Australia, there was no evidence to support criticisms that the higher incidence among Indigenous children was a result of bias in diagnosis [11]. The higher risk of SIDS among Indigenous groups has not decreased as dramatically as those among populations of European origin. Among African American infants, it has been noted that the magnitudes of the differences in deaths as a result of respiratory infections were similar to those for SIDS [12]. Although cultural and child-rearing practices and socioeconomic factors have been proposed to explain the differences between ethnic groups, there are no definitive data to account for the differences reported.

Among Indigenous groups and African Americans, there is a higher proportion of SNP associated with high levels of proinflammatory responses such as IL-6 and IFN-γ. There are also higher incidences of SNP associated with low levels of the anti-inflammatory cytokine IL-10 (**Table 6**). Not all studies agree on the effects of the polymorphisms on levels of cytokine responses to various stimuli. This could be a result of differences in the model systems examined or other environmental factors. These will be explored further in the next section about control of inflammatory responses.

Gender

In some studies, there are almost twice as many males as females classified as SIDS deaths. Males have been reported to have higher IL-6 responses than females [134]—findings that we have recently confirmed [135]. The outcome of sepsis was reported to be better in females than males, and studies about endotoxin-stimulated peripheral blood mononuclear cells from Japanese donors indicated that the major difference between responses of cells from males and females was lower production of IL-10 in the males [136]. Among renal transplant recipients, urinary tract infections elicited high anti-inflammatory responses in females compared with high proinflammatory

TABLE 6. Frequencies of SNP Associated with High (H), Intermediate (I), and Low (L) Cytokine Responses [129–133]

Cytokine	Caucasian	Bangladeshi	Australian Aboriginal	Canadian Aboriginal	American Black
SNP %	H, I, L	H, I, L	H, I, L	H, I, L	H, I, L
IL-6 G-174C	42, 41, 17	94, 6, 0	88, 11, 1	86, 14, 0	83, 16, 1
IFN-γ T+874A	16, 47, 37	13, 50, 38	39, 49, 12	4, 20, 76	9, 52, 39
IL-1B C-511T	9, 42, 49	56, 34, 9	71, 24, 6		
IL-10 G-1082A	29, 39, 31	0, 16, 84	0, 17, 83	6, 32, 62	12, 43, 45

responses in males [137]. Animal models indicate that following hypoxia, male mice had significantly higher proinflammatory responses (IL-6 and TNF-α) but not females [138]. Inflammatory responses of rat ileal mucosal membranes exposed to normoxia were compared with responses elicited after 40 min of hypoxia and/or acidosis. Each of the conditions tested induced significant increases in proinflammatory responses by tissues from males compared with tissues from females. Female tissues produced higher levels of anti-inflammatory responses (NO and IL-10), and there was less evidence of mucosal injury. Estradial or testosterone receptor antagonist treatment of male rats decreased gut injury and IL-6 and macrophage inflammatory protein-2 responses [139].

Control of inflammatory responses

Fatality of infection can be linked to high levels of proinflammatory cytokines; therefore, factors that affect their control need to be considered. In relation to infections and SIDS, there are three major categories to be considered: developmental stage, antibody levels, which are at their lowest during the 2- to 4-month age range and night-time cortisol levels that change dramatically during this period; genetic control of pro- and anti-inflammatory responses; and environmental factors, such as virus infection, overheating, or exposure to cigarette smoke.

Developmental factors

Antibody levels and the protective effects of immunization

As noted above, no, or negligible, levels of antibodies to common bacterial toxins have been detected in sera of SIDS infants compared with live, healthy control infants of the same age [37, 38]. In vitro experiments found IgA antibodies to TSST, SEC, and the enterotoxin A of *C. perfringens* present in human milk. These might neutralize the activities of the toxins before they could diffuse from mucosal surfaces. Pasteurized cow's milk contains antibodies to the staphylococcal toxins, but infant formula preparations do not [140]. Among women in the childbearing age range, British–Asian women had higher levels of total IgG and IgG specific for some of the staphylococcal toxins than women of European origin [141, 142]. Based on the predictions of the common bacterial toxin hypothesis, these higher levels of antibodies could contribute to low levels of SIDS among Asian infants in Britain. They start life with higher levels of maternal antibodies against toxigenic bacteria in their environment. Indigenous Australian infants also have significantly higher levels of IgG at birth compared with non-Indigenous infants [143]. Antibodies specific for bacterial toxins implicated in SIDS in sera of Aboriginal Australian infants have not been assessed.

Careful epidemiological studies were carried out following suggestions in the 1980s that immunization triggered SIDS. Major studies in the United States and Britain found that immunization of infants against diphtheria, pertussis, and tetanus (DPT) is associated with protection against SIDS [22, 23]. A year prior to the start of the national campaign in Britain to reduce the risk factors for SIDS in October 1991, there was a major change in infant care practices. In October 1990, childhood immunization, including DPT, was initiated at 2 months rather than 3 months of age for all British infants. Following the change in immunization schedules, there was a significant decrease in SIDS deaths among infants over 2 months of age. The greatest reduction in SIDS deaths in Scotland, England, and Wales was noted at 4 months of age, a pattern that might reflect a booster effect following primary immunization at 2 months of age, followed by further inoculations at 3 and 4 months [144, 145]. A similar trend was observed in Hungary [146]. Another suggestion is that the protective effect of early immunization might be a result of earlier switches in the T helper cell type 1 (Th1)/Th2 T cell cytokine pattern of responses [147]. In rabbits, the DPT vaccine induced antibodies to the pertussis toxin and also IgG antibodies cross-reactive with some of the pyrogenic staphylococcal toxins identified in SIDS infants [144].

Development of circadian rhythm, cortisol levels, and the predominance of night-time SIDS deaths

The majority of SIDS deaths occurs at night or the early hours of the morning, especially those in which there is evidence of infection or exposure to cigarette smoke [19]. The peak incidence of SIDS occurs during the 2- to 4-month age range, a period in which infants undergo the developmental switch to circadian rhythm, usually between 7 and 16 weeks of age. This physiological switch is detected in many studies by determination of the age at which the core body temperature of infants falls at night to 36.4°C, similar to that of sleeping adults. The period prior to the development of circadian rhythm is suggested to be an "immature" state, as infants who remain in this state for prolonged periods share many of risk factors with SIDS infants [148]. Evidence against this hypothesis comes from later work. Asian infants stay in the immature state significantly longer than infants of European origin [149], and Asian infants in Britain have a lower incidence of SIDS than infants of European origin [5].

In conjunction with the change in body temperature rhythm, there is a dramatic drop in night-time, but not day-time, cortisol levels, the week following the temperature switch. Cortisol suppresses a broad range of inflammatory responses, and during the first 2 months of life, there is a steady decrease

in plasma cortisol levels [150]. Peak responses of TNF-α, IL-1, IL-6, and IFN-γ to infectious agents occur during late evening or early morning when cortisol levels are lowest and the time during which most SIDS deaths occur [151, 152]. Cortisol levels similar to those present at night-time in infants following the developmental switch (<5 μg dl^{-1}) had little or no effect on proinflammatory responses (IL-6 and TNF-α) elicited from human leukocytes stimulated with TSST; however, levels >10 μg dl^{-1}, found during the day or at night before the physiological changes, reduced proinflammatory responses [153].

In infants, rectal temperature increased significantly the night following immunization for DPT and *H. influenzae* type b. Infants in the immature developmental state had a significant increase in urinary cortisol excretion at night and the morning after immunization. Once the circadian pattern had developed, immunization no longer caused an increase in cortisol output [154].

The period during which there are low levels of night-time cortisol could be a window of vulnerability for SIDS. If the low levels of cortisol occur when the infant has low levels of IgG, exposure to bacterial toxins with superantigen activities might result in high levels of proinflammatory responses. Remaining in the immature developmental stage for a longer period would have several advantages in relation to susceptibility to inflammatory responses as a result of what would normally be considered minor infections. The high levels of cortisol could contribute to control of inflammatory responses over a longer period, thereby allowing more time for the infant to produce active immunity to environmental bacteria and their products or to make antibodies in response to childhood immunizations, which commence at 6–8 weeks of age.

Interactions between genetic and environmental factors affecting inflammatory responses

For studies about the genetics of inflammation, the most serious confounding factor is ethnicity [155]. The importance of matching cases and controls for ethnicity is essential to prevent false findings for epidemiological and experimental studies. Studies about the association between SNP and levels of cytokines induced by exposure to various stimuli have provided conflicting data. In experimental studies in which ethnicity has been matched carefully, it is not always possible to control for asymptomatic, chronic infection or the prodromal stage of an infection in which physiological changes have occurred that could alter cytokine responses before overt symptoms are apparent in the donor. Time of day during which blood is collected must be standardized to control for the effects of cortisol in relation to circadian rhythm. Exposure to environmental pollutants such as cigarette smoke also needs to be considered. For nonsmoking adults or young children, effects of passive exposure to cigarette can only be assessed accurately by estimation of cotinine in body fluids.

IL-1β polymorphisms

IL-1β has been implicated in the pathogenesis of SIDS in experimental studies in animal models [45, 128]. It is a powerful cytokine that can affect several of the physiological responses postulated to contribute to sudden infant death—vascular shock, hypoglycaemia, deep sleep and prolonged apnoea, cardiac irregularities, and fever [84]. Parents of SIDS children were found to have significantly higher levels of IL-1β in response to bacterial toxins [85].

Among populations such as Aboriginal Australians, there is a higher incidence of SIDS and classical infections such as meningococcal disease and otitis media for which immunization is not available [156]. Fatal meningococcal infections have been associated with the IL-1B C-511T polymorphism TT genotype [157], which results in the overexpression of IL-1β [158]. There were no differences in the distribution of the IL-1B C-511T polymorphism between Bangladeshi and Aboriginal Australian groups; however, both of these showed a significant difference in the distribution compared with Europeans ($P=0.000$; Table 6). The homozygote genotype (CC), predominant among Europeans, was rare among the other two ethnic groups. Leukocytes from European subjects with the TT polymorphism, who were smokers, produced the highest median IL-1β responses to TSST and endotoxin; however, the numbers were too small for statistical analysis [134]. Other studies, which assessed the effect of smoking but not genotype, found enhanced IL-1β responses to endotoxin among smokers [127].

IL-6 polymorphisms

In a Norwegian study, half of the SIDS victims had elevated levels of IL-6 in their CSF [36]. The concentrations of IL-6 in SIDS infants were comparable with those found in infants dying from infectious diseases such as meningitis and septicaemia. The laryngeal mucosa in SIDS victims with high levels of IL-6 in the CSF also showed signs of immune stimulation with increased numbers of IgA immunocytes and increased expression of human leukocyte antigen-DR in the epithelium [159]. Many of these infants also showed signs of infection prior to death and were found dead in a prone position.

The only SIDS group for whom we had reliable, local control data was the Australian population, in which the genotypes for SIDS infants were compared with those for parents who had not had a SIDS death in their immediate families. The allele frequencies for the IL-6 G-174C polymorphism for the Australian control population differed significantly from that observed for Australian SIDS infants ($\chi^2=8.6$, df=2, $P=0.02$); only 24/63 (38%) controls had the high, proinflammatory GG genotype compared with 11/19 (58%) SIDS infants [135]. For a second set of 47 SIDS infants from Germany, we compared the distribution of genotype frequencies with those for a healthy, control population for a study of the role of IL-6 polymorphisms in sepsis. The frequency of the GG genotypes for the 47 SIDS infants (17%) was intermediate between the control (32.4%) and sepsis (8%) groups; however, the differences were not significantly different {$\chi^2=4.68$, df=2, $P<0.1$; ref. [135], unpublished results}. There were no differences in the distribution of the IL-6 G-174C polymorphism between Bangladeshi and Aboriginal Australian groups; however, both of these showed a significant difference in the distribution compared with Europeans ($P=0.000$; Table 6).

There have been variable reports about the correlations between genotype and IL-6 responses. Cells from individuals with the GG genotype of the IL-6 G-174C SNP produced higher

levels of IL-6 in vitro. Transfection of the IL-6-174C allele into HeLa cells resulted in lower levels of IL-6 compared with responses elicited by the IL-6-174G allele [160]. For leukocytes from cord blood of neonates, higher levels of IL-6 were associated with the CC genotype. No significant association between IL-6 responses and genotype was observed with leukocytes from adults [161]. In experiments with leukocytes from adults, risk factors for SIDS (e.g., cigarette smoke) might be confounding factors for some of these studies. To our knowledge, our studies are the first to assess cytokine responses in relation to smoking, gender, and genotype.

Cigarette smoke

In our recent studies, the highest median IL-6 responses to endotoxin were observed for smokers with the GG genotype. Higher median levels of IL-6 were not observed among nonsmokers for this genotype compared with those with the GC or CC genotypes. The median IL-6 responses to endotoxin for smokers with the GG genotype were significantly higher than those for nonsmokers with the same genotype ($P<0.05$) and for smokers of the other two genotypes (GG vs. GC, $P=0.01$; GC vs. CC, $P=0.00$). For nonsmokers, there were no differences between median IL-6 responses among the GG, GC, or CC genotypes [136].

Gender

Male gender was associated with increased levels of IL-6 [134]. The median IL-6 level for the 60 females tested was 4.9 ng ml^{-1} compared with 8 ng ml^{-1} for the 40 males; however, the difference was not significant. Smoking was noted to be a confounding factor. Median IL-6 levels for nonsmokers were significantly lower ($P<0.03$) for females (n=34, 5.2 ng ml^{-1}) compared with males (n=24, 8.1 ng ml^{-1}). Median IL-6 levels for smokers were not significantly lower for females (n=25, 4.6 ng ml^{-1}) compared with males {n=15, 7.85 ng ml^{-1}; ref. [135], unpublished results}.

Hyperthermia

In an infant rat model, hyperthermia significantly increased production of IL-6. Increased temperature did not, however, further enhance IL-6 responses to MDP [127].

IL-10 gene polymorphisms

IL-10 plays an important role in control of proinflammatory responses. The genetic background of an individual is thought to determine between 50% [162] and 75% [163] of IL-10 responses to endotoxin. In animal models, it reduces the lethality of staphylococcal toxins [165]. With one exception [165], the IL-10 G-1082A polymorphism in the promoter region has been associated with decreased IL-10 production [166–168]. The differences between the genotypes were not always significant, but this might be a result of small numbers of subjects in most studies.

Evidence from studies about a small number of British SIDS infants suggested there was an excess of IL-10 polymorphisms associated with lower levels of IL-10, IL-10 G-1082A, and IL-10 C-592A [169, 170]. Another study about a larger sample of Scandinavian SIDS infants found no association with any IL-10 polymorphisms [171, 172]. Our studies, like those of the Scandinavian survey, found no significant differences in the distribution of these genotypes among SIDS infants compared with controls [132]. There were no differences in the distribution of the IL-10 G-1082A polymorphism between Bangladeshi and Aboriginal Australian groups; however, both of these showed a significant difference in the distribution compared with Europeans ($P=0.000$; Table 6). The proportion of individuals with the homozygous genotype (GG) prevalent among Europeans was significantly lower among Bangladeshis and Aboriginal Australians. The homozygous genotype (AA) found in ~30% of European populations was predominant in the other ethnic two groups (>80%).

In contrast to the predictions based on the British study, baseline levels of IL-10 of SIDS parents were increased compared with those of control parents. In addition, there were no significant differences between IL-10 responses of SIDS and control parents to TSST or endotoxin. The most important finding in these studies was that smokers had significantly lower levels of IL-10, baseline levels, and those measured in response to toxin stimulation [85]. When the genotypes were assessed in relation to smoking, leukocytes from Europeans with GA or AA genotypes showed significantly lower levels of IL-10 in response to low levels of endotoxin [132], which induced significantly lower median levels of IL-10 from leukocytes from smokers (25.6 ng ml^{-1}, range 1–171.4 ng ml^{-1}) than from nonsmokers (57.7 ng ml^{-1}, range 1–1608.0 ng ml^{-1}; $P=0.00$). There were no significant differences for IL-10 responses from leukocytes from nonsmokers to endotoxin for the three genotypes of the IL-10 G-1082A SNP. There were significant differences between smokers and nonsmokers for individuals with the GA genotype ($P=0.04$) and the AA genotype ($P=0.01$). The difference between smokers and nonsmokers for the GG genotype was not significant ($P=0.09$) [132].

If these responses are similar to those that occur in vivo, the differences in the lower proportions of Bangladeshi women who smoke (3%) [173] compared with Aboriginal Australian women (75%) [174] could be an important factor in explaining the differences in their respective SIDS rates and susceptibility to severe respiratory tract infections. This is particularly important, as it has been observed that some infants have cotinine levels equivalent to those found in active smokers [109]

CONCLUSIONS

Disturbances in the balance of the inflammatory responses contribute significantly to tissue damage or fatality in response to infectious agents or their products. The responses associated with invasive bacterial conditions, such as sepsis, are thought to reflect an imbalance in which high anti-inflammatory responses and low proinflammatory responses are dominant [163]. For some SIDS infants, our hypothesis is that the responses that lead to death reflect powerful, proinflammatory responses and suppression of anti-inflammatory responses such as IL-10 by genetic makeup and interactions with environmental risk factor such as cigarette smoke. This hypothesis provides testable models that can be used to explain how the risk factors for SIDS make infants more vulnerable to sudden death, the findings at autopsy, and potential explanations for the

TABLE 7. Risk Factors for SIDS among Different Ethnic Groups (Adapted from Ref. [176])

Factor	Caucasian European	Bangladeshi	Aboriginal Australian
SIDS/1000 live births	2	0.3	6.1
Prone sleeping	+	−	−
IgG levels at birth	+	++	++
Bed-sharing	+	+++	+++
Switch to circadian rhythm (age in weeks)	8–16	12–20	?
Breastfeeding	+	+++	+++
Bacterial colonization	+	?	+++
Mothers who smoke (%)	25	3	75
High IL-6 SNP (%)	42	94	88
High IL-1β SNP (%)	9	56	71
High IFN-γ SNP (%)	16	13	39
Low IL-10 SNP (%)	31	84	83

−, +, ++, +++ = Rare to common; ? = not known.

reasons underlying the success of the public health campaigns in reducing the incidence of SIDS in many populations. In Norway, the most significant decrease following its SIDS awareness campaign was among infants between 2 and 4 months of age who had signs of infection before death [175].

A summary of the risk factors for ethnic groups with low, medium, and high incidences of SIDS is provided in **Table 7**. If cytokine gene polymorphisms were the main factor in susceptibility to SIDS, the incidence of these deaths should be similar for Aboriginal Australians and Bangladeshis. Genetic predisposition to strong proinflammatory responses is insufficient to explain the risk for SIDS; other genetic or environmental cofactors are required. Currently, the major modifiable risk factor for SIDS is exposure of infants to cigarette smoke. Among groups in which the incidence of SIDS is high, the proportion of mothers who smoke is higher than those groups in which there is a low incidence of SIDS and a low incidence of maternal smoking.

The findings from these studies are also applicable to explaining how risk factors for infection, particularly exposure to cigarette smoke, increase susceptibility to or severity of diseases such as meningitis or respiratory infections. Analysis of findings from the Scandinavian SIDS study found the risk of SIDS among infants with an infection, and the modifiable risk factors—prone sleeping, head covered, or parental smoking—were far greater than the sum of each individual factor. "These risk factors thus modify the dangerousness of infection in infancy" [20].

Perhaps the most important results are those that indicate inflammatory responses of leukocytes from donors with different genotypes are affected to varying degrees by exposure to cigarette smoke. The models developed can be applied to testing the effects of other environmental factors which could affect pro- and anti-inflammatory responses associated with different gene polymorphisms, e.g., air pollutants and virus infections. Evaluation of the effects of smoking might help to explain discrepancies in results reported by different groups for cytokine responses associated with particular gene polymorphisms.

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