Sudden Infant Death Syndrome: From Epidemiology to Pathophysiology

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Glossary

Apparent life-threatening event (ALTE): ALTE is defined as an episode that is frightening to the observer and that is characterized by some combination of apnea, color change, marked changes in muscle tone, choking or gasping, and an apparent need for resuscitation by vigorous stimulation or mouth-to-mouth ventilation.

Sudden infant death syndrome (SIDS): SIDS is defined as the sudden death of an infant under 1 year of age that remains unexplained after a complete postmortem examination, including an investigation of the death scene and a review of the case history.

Definition

Sudden infant death syndrome (SIDS) is defined as the sudden death of an infant under 1 year of age that remains unexplained after a complete postmortem examination, including an investigation of the death scene and a review of the case history. A new definition was proposed in 2004 to incorporate positive criteria such as the occurrence of death during sleep and the relatively narrow age range of death between the 3rd week to 9th month of life.

Pathologic Examinations

The results of the postmortem investigations in SIDS are by definition insufficient to explain the cause of death. In most infants dying suddenly and unexpectedly during sleep, the autopsy findings were very subtle and yielded only supportive rather than conclusive findings. Autopsy studies demonstrated structural evidence or tissue markers of asphyxia in nearly 75% of SIDS subjects. A complete pathologic examination is required for the diagnosis of SIDS, including microscopic, toxicological, microbiological, immunohistochemical, molecular, and metabolic exams. These postmortem investigations let to identify a medical or surgical origin of death in 15–50% of cases depending on the number of investigations performed.

Incidence

In the early 1990s, the incidence of SIDS was estimated between 1 and 3 per 1000 live births for most industrialized countries. There has been an over 50% reduction in the incidence of SIDS since the American Academy of Pediatrics (AAP) released its recommendation in 1992 that infants have to be placed down for sleep in a nonprone position. Infants dying of SIDS still constituted the largest component of postneonatal infant mortality, accounting for approximately 30% of postnatal deaths (between 28 days and 1 year). In a recent review of SIDS data from 13 predominantly industrialized countries, the majority of countries had a major decrease in SIDS rates from 1990 to 2005, with the largest decreases occurring before 2000. The true incidence of SIDS may be masked by a so-called diagnostic shift, or the use of diagnoses other than SIDS on death certificates (e.g., accidental suffocation, positional accidental asphyxia, and indeterminate cause). Diagnostic shift may explain, in part, why postneonatal death rates for both SIDS and non-SIDS have remained static since approximately 2000.

Most deaths from SIDS occur in the first 6 months of life, with a specific peak between 2 and 4 months of age. The deaths occur during sleep, during nap, or during night sleep. Male infants have a 50% increased risk of dying of SIDS than female infants. In 10% of cases, SIDS victims had experimented an apparent life threatening event some days or weeks before their death. The surviving infant is usually considered to have 5–10% increased risk of dying of SIDS. The reported rates of SIDS differ greatly among various countries, ranging from 0.05 in Japan to 0.75 in the United States. The discrepancy could result from a variety of causes. Incomplete or absent postmortem examination, inexperienced pathologists, differences in classification of causes of deaths can lead to potential misclassification of causes of deaths.

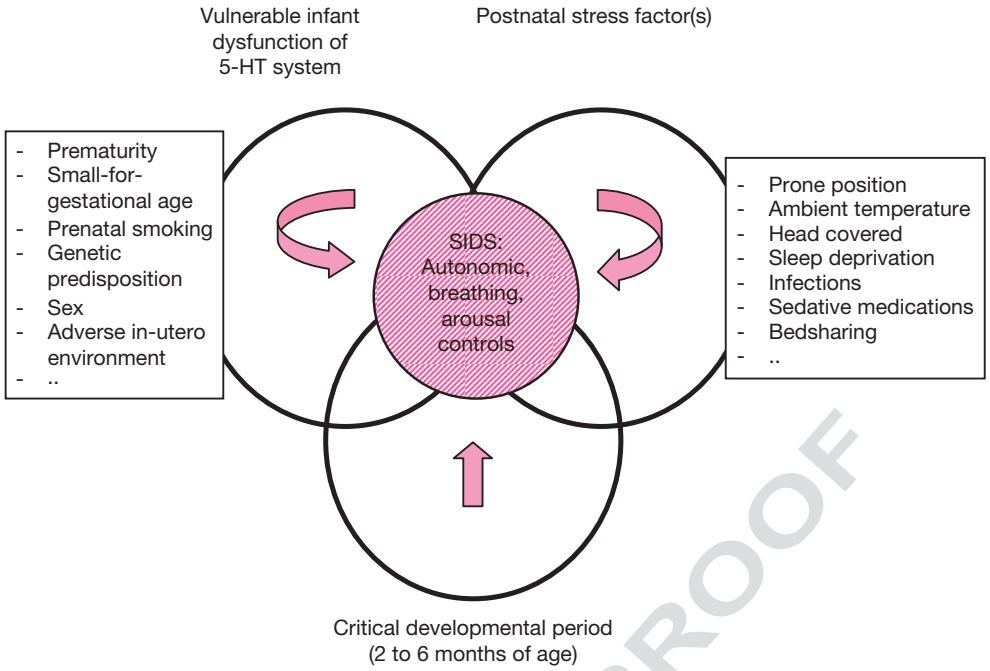
Risk and Protective Factors

A number of factors have been found to be associated with increased (and decreased) SIDS risk (Figure 1).

Sociodemographic and Climatic Factors

Socioeconomic class

An increased risk for SIDS was related to a lower socioeconomic status, measured by the parents' occupation, income, or education. After the information campaigns, the proportion of SIDS deaths occurring in families living in poverty has increased from 47% to 74%. Migrant populations, families of



f0010 **Figure 1** SIDS potential factors. The diagram of three overlapping circles represents the triple-risk model for SIDS. According this model, SIDS results from the intersection of three overlapping factors: (1) underlying vulnerability in the infant; (2) a critical period in homeostatic control; (3) an exogenous stressor(s). 5-HT system: medullary 5-hydroxytryptamine system. Adapted from Filiano JJ and Kinney HC (1994) A perspective Au1,2 on neuropathologic findings in victims of the sudden infant death syndrome: The triple-risk model. *Biology of the Neonate* 65(3–4): 194–197.

low social classes, young mothers (<20 years), mothers with a minimum level of education (<11 years), and noncohabiting mothers are particularly resistant to changes in infant care practices and have the highest prevalence rates of these risks factors.

s0040 ### *Race and geography*

p0040 A striking discrepancy exists among racial and ethnic groups that have been studied, with SIDS rates that are two to seven times the national averages among Native Americans and blacks in the United States; among Maoris in New Zealand; and among aboriginal Australians. Genetic influences, cultural practices of child care, or socioeconomic factors could all be responsible for the differences in racial risk ratios.

s0045 ### *Season and climate*

p0045 The cold weather months could have an effect on SIDS rates through multiple associated risk factors, such as infectious agents, nutritional or metabolic processes, infant care practices, excessive ambient temperature in the infants' room, or other life-style factors. In countries where campaigns to reduce environmental risks have been conducted, the seasonal discrepancy of SIDS incidence has markedly decreased.

s0050 ## Perinatal Risk Factors

s0055 ### *Prematurity and fetal growth retardation*

p0050 The relative risk of SIDS incidence is four to six times higher in infants born prematurely. The relative risk increases as gestational age decreases. In utero growth retardation is also a major risk factor. The incidence is estimated to be 8.7 per 1000 live births in premature infants of less than 1500 g. After the preventive campaign, the demographic characteristics associated with SIDS have changed with a decrease in the proportion of SIDS deaths occurring in term infants, whereas the proportion in preterm infants has increased from 12% to 34% in United Kingdom.

Maternal and antenatal risk factors: cigarette smoking, alcohol, and other drugs s0060

p0055 Epidemiological surveys confirmed that smoking is associated with an increased risk of SIDS with a risk ratio of between 1.7 and 4.1. This risk ratio is dose dependent and is mainly associated with prenatal maternal smoking, and to a lesser extent, to postnatal exposure to cigarette smoke. After preventive campaign, the prevalence of maternal smoking increased among the SIDS deaths from 57% to 87% and is become the most important modifiable risk factor for SIDS.

p0060 The risk for SIDS in infants of mothers addicted to drugs (marijuana, methadone, cocaine, heroin) is higher than that for the general population. Parental alcohol use during pregnancy is likely associated with increased SIDS risk and can act synergistically with other substance use. Postnatal alcohol use also appears to be implicated, particularly when combined with bedsharing.

SIDS recurrence rates s0065

p0065 The recurrence rate for siblings of SIDS victims could be three to six times higher than that in the nonselected population. Such studies of recurrence have been criticized for not

considering the possibility of serial infanticide. However, second deaths were not rare (6.2 per 1000 living births) and the majority of deaths, 80–90% were natural. The risk for twins appears to be at least twice as high as that for a subsequent sibling. First cousins and other members of a SIDS family share the same risk as the general population.

s0070 ## Sleep Environment

s0075 ### *Prone sleeping position*

p0070 Case-control reviews on sleeping position and SIDS showed that the relative risk for SIDS increased four- to ninefold when infants sleep prone than when they sleep supine. The reduction in mortality after the preventive campaign has been mainly attributed to the avoidance of the prone sleep position. The prone sleeping position has dropped from 70% in 1992 to less than 10% in 2004, and has led to an over 50% reduction in postneonatal mortality and frequency of SIDS. Inexperienced prone sleeping was determinant for SIDS. The infants who were usually placed nonprone but were placed prone for last night had the higher risk ratio than infants who were placed prone usually. Infants who are inexperienced in prone sleeping have decreased ability to escape from asphyxiating sleep environments when placed prone. The combination of prone positioning and the use of soft bedding further increased the risk of dying, probably because the nose and mouth were often being trapped and covered, or because of reduced carbon dioxide dispersal. Side sleeping position is an intermediate risk factor between prone and supine position. The infants placed on the side have more probability to roll over the prone position.

s0080 ### *Bed coverings, overheating, and head covering*

p0075 Hyperthermia due to overdressing or to a high environmental temperature was suggested to be a risk factor for SIDS. Most SIDS victims were reported to be overdressed and overdraped at the time of death. For every thermal insulation unit (or Tog value), the relative risk for SIDS increased by 1.26. A combination of factors seems important to create hyperthermia, such as soft bedding combined with the use of a duvet. In a systematic review of population-based age-matched controlled studies, more than a quarter of SIDS were found with their heads covered with bedclothes. Being found with head covering was associated with older infant age, which probably reflects motor development.

s0085 ### *Bedsharing*

p0080 Besharing is associated with an increased risk of SIDS not only for infants from smoking mothers but also for infants from nonsmoking mothers younger than 8–11 weeks. In a recent study, Blair et al. found that the median age at death was more than 3 weeks less than in a study in the same region a decade earlier and that more than 50% of SIDS died while cosleeping. The risk associated with maternal smoking, alcohol or sedative drug consumption, low birth weight, and wrapping in excess was augmented by bedsharing. Couch sharing was associated with the highest risk for SIDS and should be discouraged at any age.

s0090 ### Infections

p0085 In 70% of cases, the sudden death was preceded, within 24 h of the time of death, by a minor illness, especially gastrointestinal or upper airway infections. Respiratory syncitial virus was reported to trigger pauses, possibly related to some life-threatening events. Recent illness appears to interact with other factors to increase the risk of SIDS. Combined effects of viral infection with prone position or with wrapping in excess produced the highest risk ratios. It was also reported that treatments for nasopharyngitis with phenothiazine drugs increased the risk for SIDS. These and other sedative drugs were associated with an increased frequency of SIDS and were shown to induce central as well as obstructive sleep apneas while decreasing the arousability of the infants.

s0095 ### Potential Protective Factors for SIDS: Breastfeeding, Pacifiers, Sleeping Bags, Firm Bedding, Swaddling, and Room Sharing

p0090 Pacifier use has been reported to be associated with a reduced risk of SIDS, especially when placed for sleep, suggesting that pacifier use should be encouraged in infants up to 1 year to prevent SIDS. The mechanisms responsible for this protective effect are not known. Other factors such as breastfeeding, sleeping bags, firm bedding could also protect against SIDS. Breastfeeding could benefit the infant by reducing the risk for intestinal infections. Sleeping bags could have a protective effect by reducing the risk of hyperthermia, head covering, and prone sleeping. Firm bedding and reduced covering were also considered useful to prevent hyperthermia and to decrease the risk of SIDS. Low risk of SIDS was also reported in infants who usually shared the parents' room. Swaddling has also been considered to reduce SIDS. The odd ratio for SIDS in swaddled infants sleeping supine has been reported to be of 0.64–0.69. The mechanisms responsible for the protective effect of swaddling are not known. Although swaddling favors sleep continuity and prevents to roll over the prone position, it is also associated with an increased responsiveness to environmental auditory stress.

s0100 ## Model for SIDS

p0095 In 1994, Kinney and Filiano suggested a triple-risk model for SIDS that includes three combined factors: an underlying prenatal vulnerability, a critical developmental period, and an exogenous postnatal stressor. The infant's vulnerability lies latent until the infant enters the critical developmental period from 2 to 6 months and is exposed to an exogenous stressor.

s0105 ### Prenatal Vulnerability

p0100 Prenatal vulnerability could be secondary to genetic alterations, adverse intrauterine environment, or due to premature birth.

s0110 ### *Genetic alterations*

p0105 The genetic component of sudden unexpected infant death (SUID) can be divided into two categories. Genetic alterations that may cause sudden infant death per se such as mutations in the medium-chain acyl-coenzyme A dehydrogenase

Au7 (MCAD) gene (±1% of SUID cases) and de novo genetic cardiac channelopathies (5–10% of SUID cases). In the other hand, genetic polymorphisms may predispose infants to sudden infant death under certain circumstances. Polymorphisms in genes involved in the immune system, in thermal regulation, or cellular energy are of importance with respect to SUID. Another gene that has been investigated is the serotonin transporter gene. The L and XL alleles were more frequently found than S alleles in SIDS victims than in age-matched control participants. The L allele is associated with increased expression of the serotonin transporter in various brain regions, and thus lower synaptic serotonin availability. The long alleles may be related to SIDS, either through downregulation of presynaptic autoreceptors or through a developmental effect on the brainstem.

s0115 ### *Adverse intrauterine environment and premature birth*

p0110 Adverse intrauterine environment during pregnancy may be another important risk for SIDS. Risks associated with placental abnormalities, maternal smoking, and preterm birth suggest an important role for factors that lead to 'hypoxic conditions' either in the fetus or in the newborn. These conditions could result in subtle neurological damage that contributes to later infant demise.

s0120 ## The Critical Development Period

p0115 Most deaths from SIDS occur in the first 6 months of life, with a specific peak between 2 and 4 months of age. This age distribution of SIDS corresponds to a period of the infant's life when significant changes occur in sleep–wake, breathing, autonomic controls, and immunological maturation. An important transitional period from principally subcortical to cortical controls occurs between 2 and 5 months of age, typically the age of greater SIDS risk. This loss of reflexive behaviors could be a risk factor if the voluntary responses are not already acquired.

s0125 ## The Role of Environmental Stressors

p0120 The importance of environmental stress factors in the development of SIDS is highlighted by the drop in SIDS incidence measured in most countries following the prevention campaigns. Environmental stressors include the prone sleep position, a high room temperature, sleeping with the face covered, prenatal maternal smoking, or drug addiction. Other stressors that modify the infant's ability to cope with the environment include previous sleep deprivation or changes in routine care. Although the prevalence of known risk factors for SIDS was more favorable in the child-care settings than at home, stress and changes in routine care could be implicated in the increased risk for SIDS in the child care settings.

s0130 ## Mechanisms Implicated in SIDS Deaths

p0125 Three basic mechanisms were postulated to cause SIDS:

o0010 1. The breathing control hypothesis.
o0015 2. The autonomic control hypothesis.
o0020 3. The sleep and arousal hypothesis.

The Breathing Control Hypothesis s0135

Infants who later succumbed to SIDS had more frequent mixed and obstructive sleep apneas than control subjects. Postmortem findings support the development of frequent hypoxic events, possibly related to airway obstructions. The mechanisms responsible for the obstructive sleep apnea are complex. In infants, obstructive sleep apneas are most frequently due to narrowed upper airways, due to nasal infection, anatomic abnormalities, neurological lesions impairing muscle contractions, or soft tissue infiltration. Narrowed upper airways could be inherited, as sleep apneas and smaller airways were also found in some SIDS family members. p0145

Infants sleeping prone and face down on soft bedding show episodes of airway obstruction. The frequency of obstructive sleep apnea is, however, not associated with body position, although the duration of the apnea increases when the infants sleep prone. The development of apnea could depend on other environmental factors. Healthy infants develop a greater frequency of obstructive sleep apneas when they are exposed to some risk conditions for SIDS, such as being born from a smoking mother, being treated by sedative medications, or having been sleep deprived. p0150

The Autonomic Control Hypothesis s0140

Future SIDS victims exhibit symptoms during sleep that reflect a subtle dysautonomia. These include episodes of profuse sweat productions during sleep, tachycardia, bradycardia, higher overall heart rate, or reduced heart rate variability. Analysis of the heart rate variability in future SIDS victims showed findings compatible with a decrease in parasympathetic, an increase in sympathetic activity, or a combination of both conditions. Such imbalance in cardiac autonomic control has been postulated to induce prolongation of the QTc interval in SIDS victims. The greater sympathovagal control seen in infants at risk of SIDS could result from a delayed maturational process or from repetitive hypoxia that modifies brainstem, cerebellar, or cortical areas involved in autonomic controls. p0155

Exposure to maternal smoking, in utero growth retardation, premature birth induce marked effects on the ANS. Compared to full-term infants, preterm infants have also been shown to have a higher heart rate and reduced heart rate variability at term equivalent age as well as lower blood pressure and baroreceptor reflex responses in sleep across the first 6 months. Autonomic cardiac controls are also dependent on postnatal environmental factors. Increases in sympathovagal controls have been measured in prone sleep, following sleep deprivation, sleeping in high ambient temperatures, or with the face covered by a bed sheet. Pacifier use, sleeping supine in swaddling condition during sleep, two factors associated with a lower risk for SIDS, were characterized by a reduction of the heart rate sympathovagal ratio. p0160 Au8

It has been reported that increased sympathetic activity reduced the electrical stability of the heart and precipitated ventricular fibrillation and sudden cardiac death. Basal parasympathetic tonus also reflects the individual's capacity to respond to stress. An attenuated vagal or an increased sympathetic activity could reduce behavioral adaptation to environmental stresses. p0165

s0145 ## The Arousal Hypothesis

p0170 The temporal association between SIDS and sleep suggests that the arousability from sleep provides a protective mechanism for survival when the infant is confronted with a life-threatening challenge during sleep. Failure to arouse could be involved in the final pathway of SIDS. Several studies have reported a developmental delay in sleep organization and a reduced frequency of awakenings from sleep in future SIDS victims, especially at the end of the sleep period (a time of peak incidence for SIDS). It has been shown that infants who became victims of SIDS not only aroused less from sleep than control infants, but that their arousals characteristics were different. Compared to control infants, SIDS victims had significantly more incomplete arousals (subcortical activation) in the first part of the night, between 9:00 p.m. and midnight, and fewer complete arousals (cortical arousals) during the latter part of the night. The data are suggestive of incomplete arousal processes in infants who eventually died.

p0175 In utero and postnatal environmental conditions can modify arousal responses. Infants of substance-abusing mothers aroused after longer exposure to hypoxia than control subjects. More infants of cigarette-smoking mothers than control infants failed to awake to environmental challenges. Prematurity is also associated with greater arousal thresholds. Postnatal environmental factors also influence arousability from sleep. Viral infections of the airways, administration of sedative drugs, a previous sleep deprivation, sleeping prone, sleeping with the face covered, or in high ambient temperatures increase arousal thresholds. Breastfeeding, pacifier use, and swaddling condition during sleep reported to decrease risk of SIDS, were also associated with lower auditory arousal thresholds.

s0150 ## Physiopathology

p0180 Alterations in breathing, cardiac, and arousal controls could result from structural or functional changes within the infants' central nervous system. Pathological and immunohistochemical studies in SIDS infants demonstrated diffuse lesions within different nuclei of the central nervous system, essentially at the brainstem level. Pathological changes described in SIDS victims include brain stem gliosis, hypoplasia, or apoptosis. To date, the most robust evidence for a neurochemical abnormality comes from research on the medullary 5-hydroxytryptamine system (5-HT), in that approximately 50–75% of infants with SIDS appear to have abnormalities in this system. These include decreased 5-HT1A receptor bindings and low serotonin values in the medulla of infants that died of SIDS. The medullary 5-HT system is considered critical for the modulation and integration of diverse homeostatic functions such as respiratory, cardiovascular, and arousal controls. 5-HT neurons of the medulla are central respiratory chemoreceptors that regulate systemic levels of PCO_2 although 5-HT neurons of the midbrain are involved in regulation of sleep and arousal. Genetically modified mice expressing a selective and near-complete reduction in the number of 5-HT neurons in the brain showed a complete lack of any arousal response to inhalation of CO_2 (with 21% O_2 in balance N_2).

p0185 In a recent study, 85% of 209 sudden infant deaths were associated with circumstances 'consistent with asphyxia,' (combined hypoxia and hypercapnia) which included a prone position and bed sharing. For example, when a blanket obstructs the mouth and nose of an infant who is asleep, an increase in respiratory effort is unlikely to provide enough air exchange to maintain normal arterial PO_2 and PCO_2. It is important to also wake up slightly and turn the head to relieve the obstruction. Moreover, in these vulnerable infants, autoresuscitation is impaired – a second defense failure – because of ineffectual gasping, which results in uninterrupted apnea and death. Gasping mechanism also required release of 5-HT to function.

p0190 'Extrinsic' and 'intrinsic' SIDS risk factors could have different implications in the sudden death of these infants. Extrinsic factors, for example, prone sleep position, are physical stressors that place a vulnerable infant at risk for homeostatic derangements, such as rebreathing of exhaled gases around the time of death. Intrinsic factors, for example, prematurity, male sex, in utero tobacco exposure are postulated to affect the underlying vulnerability in the infant, that is, in decreasing 5-HT1A receptor binding density. The 5-HT defect is likely due to developmental delay in maturation of 5-HT neurons due to environmental or genetic causes.

s0155 ## Conclusion

p0195 These findings could contribute to understanding some mechanisms favoring the unexpected death of an infant during sleep. An infant could be vulnerable for SIDS because of a deficiency in cardiorespiratory controls during sleep, favoring the development of recurrent episodes of hypoxemia. The risk is increased when the vulnerable infant has also a lower propensity to arouse from sleep and to autoresuscitate. Dysfunction in the 5-HT system has been implicated in the vulnerability of these future SIDS infants. The accident has a greater probability of occurring when an infection, or an unfavorable environmental stress factor aggravates the immature cardiorespiratory and sleep/wake behaviors of the infant. Proinflammatory cytokines could interfere with neurotransmitters in those critical brainstem centers, causing disturbed homeostatic control of cardiorespiratory and arousal responses, possibly leading to SIDS. Maturation of cortical arousal process indicated that critical development period could be a vulnerable period for arousability.

p0200 Various environmental factors thus modify the vital cardiocirculatory, respiratory, and arousal controls in healthy infants (Table 1). Similar changes in cardiorespiratory and autoresuscitative responses have been found in the analysis of sleep recordings of victims of SIDS. It is not known why some infants died, while others show similar changes but survive the first year of life. The death could be due to the degree of the initial immature controls, to the severity of the additional challenge, or to a combine effect of inadequate autoresuscitative mechanisms and the cumulative influence of infant and/or environmental stressors.

p0205 Most environmental risk factors are modifiable risk factors. They are present in 30–80% of future SIDS victims. Their avoidance contributes to the development of safe sleep environments and reduces the risk for SIDS by the continuous information of health professionals and the public. Special

t0010 **Table 1** Environmental factors – SIDS

Infants exposed to risk factors for SIDS						*SIDS victims*	*Protective factors*	
	Prone	*Maternal smoking*	*⇑ Ambient temperature*	*Covered face*	*Sleep deprivation*		*Pacifier breastfeeding*	*Swaddling supine*
Breathing controls								
Obstructive apnea		⇑			⇑	⇑		
Cardiac autonomic controls								
PS	⇓	⇓	⇓	⇓	⇓	⇓	⇑	⇑
OS		⇑			⇑	⇑		
Sleep/wake behavioral controls								
Arousals	⇓	⇓	⇓	⇓	⇓	⇓	⇑	⇑

PS, parasympathetic tonus; OS, orthosympathetic tonus.

efforts must be addressed to populations at higher risk, such as those poorly influenced by usual prevention campaigns. These include mothers of low education, immigrant families, or families of lower socioeconomic status. Attention should also be focused on most determinant risk factors, such as maternal smoking and prematurity.

Au9, 10 ## Further Reading

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Abstract:

Despite the dramatic decline in the incidence of sudden infant death syndrome (SIDS) by 50–90% over the past two decades, SIDS continues to be the leading cause of death in infants aged between 1 month and 1 year in developed countries.

We will review the most recent epidemiological, electrophysiological, genetic, and pathological research on this topic. From these data, a comprehensive model for SIDS has been proposed: the death would result from the combination of three factors (a prenatal vulnerability, a critical developmental period, and an exogenous postnatal stress) and three potential mechanisms (deficiencies in breathing, autonomic, and sleep–wake controls).

An infant could be vulnerable to SIDS because of a deficiency in the medullary 5-hydroxytryptamine (5-HT) system due to environmental or genetic causes. This system has a key role in homeostatic functions involving respiratory, cardiovascular, and arousal controls. The infant's vulnerability lies latent until he/she enters the critical developmental period from 2 to 6 months when significant changes in sleep–wake, breathing, and autonomic controls occur. The accident has a greater probability of occurring when the infant is exposed to an infection, or an unfavorable environmental factor which enhances the immature cardio respiratory and sleep/wake behaviors of the infant.

Keywords: Infant; Risk factors; Sleep; Sudden infant death syndrome

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