Published in final edited form as:

Biol Res Nurs. 2009 October ; 11(2): 187–194. doi:10.1177/1099800408324854.

Is Shock a key element in the pathology of Sudden Infant Death Syndrome (SIDS)?

Jane Blood-Siegfried^{*}, Margaret T. Bowers [Assistant Clinical Professor], and
Duke University School of Nursing bower005@mc.duke.edu

Marcia Lorimer [Assistant Clinical Professor]
Duke University School of Nursing lorim001@mc.duke.edu

Abstract

In developed countries Sudden Infant Death Syndrome (SIDS) is the most common cause of death for infants between the age of 1 month and 1 year. The etiology of SIDS is likely to be multifactorial, and current paradigms often describe three overlapping elements of risk. Those elements are a critical developmental period, a vulnerable infant and one or more exogenous stressors.

In the “Triple-risk Model”, SIDS infants are described as having an underlying vulnerability in cardio-respiratory control in the central nervous system during a critical period when autonomic control is developing. This vulnerability might affect the response to exogenous stressors, including prone sleep position, hypoxia and increased carbon dioxide.

In the “Common Bacterial Hypothesis” and “Fatal Triangle”, the focus is on the stressors. A combination of common respiratory infections can cause SIDS in an infant during a developmentally vulnerable period. This theory also includes three factors of vulnerability: a genetic predisposition, vulnerable developmental age and infectious stressors. In the “Fatal Triangle” theory, infection, inflammation and genetics each play a role in triggering a SIDS fatality.

From our work in an animal model we have found that rat pups die from a combination of infectious insults, during a critical time of development. This is exacerbated by perinatal nicotine exposure, a condition shown to alter the autonomic response in exposed offspring. We are proposing that shock and cardiovascular collapse is a key element that links these theories.

Keywords

SIDS; shock; infection; nicotine

Introduction

In developed countries Sudden Infant Death Syndrome (SIDS) is the most common cause of death for infants between the age of 1 month and 1 year. SIDS is a diagnosis of exclusion used to describe the sudden and unexpected death of an infant when no other plausible cause can be found (Beckwith, 1970). Factors such as maternal smoking, prone sleeping, infection, lack of breastfeeding and overheating have all been associated with SIDS mortality. Several theories have been proposed to explain the sudden deaths in this age group; however, the mechanisms responsible for SIDS remain poorly understood.

^{*}Corresponding author DNSc, CPNP Associate Clinical Professor Duke University School of Nursing DUMC Box 3322 Durham, NC 27710 Ph.: (919) 668-3837 Fax: (919) 681-8899 blood002@mc.duke.edu .

SIDS research comprises a wide diversity of topics including the examination of the brain stem for pre-existing defects that could be exacerbated by hypoxic episodes in infants (Kinney, Filiano, & White, 2001). Some researchers have focused on the role of infectious insults in SIDS (Blackwell et al., 2004; Blood-Siegfried et al., 2004; Blood-Siegfried et al., 2002; Morris, 1999; Morris, Haran, & Smith, 1987), while other researchers have described anomalies in cardiac function and rhythm, inborn errors of metabolism and heat shock stress (Burchell, Lyall, Busuttil, Bell, & Hume, 1992; Dunder, Lanyon, & Connor, 1993; Gozal, 1996; Hodgman & Siassi, 1999; Maron, Clark, Goldstein, & Epstein, 1976; Sawczenko & Fleming, 1996). More recent exploration has involved finding specific genetic abnormalities in SIDS infants (Blackwell et al., 2004, 2005; Fifer & Myers, 2002; Gordon et al., 2002; Rognum & Saugstad, 1993).

The etiology of SIDS is likely to be multifactorial, and similarities between the proposed factors could be helpful in planning research. Current paradigms often involve three overlapping elements that, when all occur, lead to SIDS. Those elements are: a critical developmental period, a vulnerable infant and one or more exogenous stressors. These three elements, though their definitions vary, tend to be common in many of the theories of SIDS (Beckwith, 1970; Kinney, Filiano, & Harper, 1992; Morris, 1999; Rognum & Saugstad, 1993; Wedgewood, 1972).

Triple-risk Model of SIDS

The brainstem is responsible for regulation of heart rate, breathing and maintaining blood pressure; thus, a defect in this area of the brain could have a fatal effect. According to the triple-risk model, SIDS infants might have an underlying vulnerability in cardio-respiratory control in the central nervous system during a critical period when autonomic control is developing. This vulnerability might affect the response to exogenous stressors, including prone sleep position, hypoxia, and increased carbon dioxide (Kinney et al., 1992; Kinney et al., 2001).

Studies of neuropathology reveal that the brains of many SIDS victims show histologic and chemical features that indicate possible abnormal development (Harper, Kinney, Fleming, & Thach, 2000; Kinney et al., 1992). These developmental abnormalities are primarily in the brain stem, but can be found throughout the brain. They reflect possible damage from anoxia, but are not limited to that particular insult.

Prone sleeping position, an important risk factor for SIDS, plays a significant role because of inadequate gas exchange; however, elevated body temperature might also be a factor. The fatal event involves an inability to compensate for a vital physiologic challenge in a neurologically compromised infant during sleep. Compensatory mechanisms such as gasping ability, arousal state, or efforts to overcome lowered blood pressure and heart rate are currently being examined (Table 1) (Harper, 2001; Harper et al., 2000).

Common Bacterial Hypothesis of SIDS

Another theory of SIDS is the “Common Bacterial Hypothesis”. This theory suggests that common bacterial toxins found in the respiratory tract, in association with a viral infection, can cause SIDS in an infant during a developmentally vulnerable period (Morris, 1999; Morris et al., 1987). Many infants who succumb to SIDS have a history of a pre-existing viral infection. Most cases of SIDS occur during the winter and spring when viral infections are most prevalent. This theory also includes three factors of vulnerability: a genetic predisposition, vulnerable developmental age and infectious stressors.

Rognum and Saugstad describe a similar theory, the “Fatal Triangle”. In this theory, infection, inflammation and genetics each play a role in triggering a SIDS fatality. Increased

inflammatory markers found in SIDS infants might be indicative of a vulnerability in the mucosal immune response to an infectious trigger in infants with a certain genetic predisposition (Rognum & Saugstad, 1993).

Prone sleeping in this model might cause impairment of gas exchange; however, there are also data to suggest that a prone position might exacerbate the response to infection. During times of viral infection, prone position can increase airway temperature, stimulating bacterial infection and bacterial toxin production (Morris et al., 1987). When nasal septal temperatures of children who had no evidence of respiratory tract infection were measured in both the prone and erect positions, they were significantly higher in the prone position (Molony, Blackwell, & Busuttill, 1999). Infants with an upper respiratory infection placed in the prone position for sleeping have been shown to have greater bacterial colonization on early morning swabs. Gram-negative bacilli, particularly *Haemophilus influenza* and *Neisseria* species, were more common than in supine sleepers, and the highest counts were measured in prone sleepers with a concurrent upper respiratory infection (Table 1) (Harrison, Morris, Telford, Brown, & Jones, 1999).

It is important to note that the majority of infants dying of non-bacterial causes in first year of life do not show signs of bacterial colonization, except in SIDS infants. The odds ratio for finding coliforms in the respiratory tract of SIDS infants is 29 compared to normal live infants (Gilbert et al., 1992). Many of these infants have signs of increased bacterial toxin production including pyrogenic staphylococcal toxins along with signs of increased inflammation and organ shock (Blackwell et al., 2002; Blood-Siegfried, Rambaud, Nyska, & Germolec, in press)

Infection

Several researchers report that viral infections can predispose to sudden unexplained death in animal models (Lundemose, Smith, & Sweet, 1993; Raza & Blackwell, 1999; Raza et al., 1999). We have established a developmental model of sudden unexplained death in neonatal rats that mirrors the common bacterial hypothesis. We have used several different combinations of insults and have found that no one insult is sufficient to cause death. There must be a combination of events to stimulate death. Two infectious insults, one viral and one bacterial, as in the "Common Bacterial Hypothesis" of SIDS, will cause death in 10-12 day old rat pups (Blood-Siegfried et al., 2004; Blood-Siegfried et al., 2002). The animals die quickly and quietly with a few minor symptoms prior to death.

In this model changes in the immune system and cardiovascular response are important. On examination, there is an increase in inflammatory markers and release of reactive oxygen species, causing a loss of blood pressure and a rapid septic shock-like episode inducing death. Tail cardiovascular measurements confirm a decrease in blood pressure. Initially, these animals have a compensatory increase in heart rate; however, this is followed by a decrease in cardiac rate, decrease in blood pressure and death. Histologic examination of tissues confirms signs of shock and thymic involution, which is also found in SIDS infants (Blood-Siegfried et al., 2004; Blood-Siegfried et al., 2002; Blood-Siegfried et al., in press; Rambaud et al., 1999)

Maternal Smoking

Maternal smoking is one of the major risk factors for SIDS. Perinatal nicotine exposure might cause developmental changes in autonomic response to cardiovascular stress. These include hypoxia, hypotension from bacterial toxin release and hypotension from heat shock. Nicotine exposure might also induce brain stem and other central nervous system abnormalities related to the response to hypoxia and cardiovascular recovery. When nicotine is administered throughout pregnancy to the rat dam in the animal model, it exacerbates the lethal response to

the two infectious insults (unpublished data). We are currently working on the hypothesis that prenatal nicotine exposure changes receptors in the brain that are important for autonomic protection. That is, nicotine exposed neonatal animals might be unable to respond to a hypotensive crisis stimulated by a bacterial toxin insult.

Another key piece of our animal model is developmental susceptibility. Ten- to twelve-day-old rat pups are most susceptible to the insults while younger and older animals do not die. We think age-related vulnerability is associated with the development of autonomic control, an increase in immune responsiveness and a normal decrease in cortisol production at this age. These animals have a rapid production of nitric oxide followed by significant hypotension caused by the two infectious insults. When they are additionally exposed to nicotine during gestation this susceptibility is accentuated. Both infection and nicotine can induce the production of nitric oxide, and prenatal nicotine exposure might have the added effect of dampening the autonomic response to hypotension and cardiovascular stress, and therefore increasing mortality.

Understanding the question of age risk is difficult. SIDS occurs between 1 month and 1 year, with peak incidence between 3 and 4 months of age. There might be a time point in development when animals and humans are more prone to problems with uncompensated basic autonomic function. Perhaps during certain times of development, the infant is incapable of mounting a protective response to physiologic stressors. If the infant was challenged during this period, he or she could succumb to a theoretically non-lethal event. Developmental vulnerability is a common theme in most theories of SIDS. Shock has not been described specifically, but in the animal model it is the result of two bacterial insults given at a specific vulnerable age.

The Physiology of Shock in Children

Shock is a condition that results in inadequate delivery of oxygen and other nutrients required to maintain healthy tissues. Initially, the body compensates by increasing heart rate; however, in uncompensated shock, the heart rate and blood pressure continue to decline. Cells are unable to maintain the metabolism necessary for function, resulting in cell death, multiple organ system failure and death (Bone, 1996).

Shock can be caused by pathological conditions that lead to decreased circulating volume, either directly, through blood or fluid loss, or indirectly, as in heat shock and infection. With sepsis, the normal peripheral vascular tone becomes inappropriately relaxed by the release of reactive oxygen species such as nitric oxide. This vasodilatation increases venous space and induces a relative hypovolemia, even in a normally hydrated subject. The resulting disruption in blood pressure increases heart rate to compensate for loss of vascular tone despite no change in vascular volume (Bone, 1996).

Bacterial infection causes a systemic inflammatory response triggered by the presence of infectious agents or their toxins. Endotoxin or gram-negative bacterial cell wall stimulates the release of inflammatory mediators and cytokines such as tumor necrosis factor- α , interleukin -1, interleukin -2, interleukin -6, and acute phase proteins involved in coagulation. The inflammatory mediators induce the production of a strong vasodilator, nitric oxide, leading to massive systemic vasodilatation. Sepsis might also result in intravascular leaking of fluid into tissue third spaces, causing an additional burden by decreasing blood volume (Bone, 1996). Circulating toxins and inflammatory mediators might also depress cardiac output by decreasing myocardial function and contractility.

Overactivation of the clotting cascade by acute phase proteins can result in altered clotting, resulting in microvascular obstructive shock, as well as hemorrhage (Schwarz, 2006). Autopsy findings observed in many SIDS infants show characteristic intrathoracic petechiae and liquid

blood in the heart. (Berry, 1992; Krous, 1984) Mast cell degranulation has been documented in some SIDS infants, and release of heparin from the granules might act as an anticoagulative factor. (Holgate et al., 1994; Platt et al., 1994) This pathology was also observed in the rat model of sudden unexplained death (Blood-Siegfried et al., 2004; Blood-Siegfried et al., 2002)

In children, hypotension during shock occurs when systolic blood pressure is less than the fifth percentile for the child's age. Cardiopulmonary failure occurs when there are global deficits in ventilation, oxygenation and perfusion. This ominous status is typically manifested by agonal respirations, bradycardia, cyanosis, weak central and nondetectable distal pulses (American Heart Association, 2005). In children, bradycardia represents decompensation, impending cardiovascular failure, and is the most common cause of death (Hazinski & Jenkins, 2002). This same pattern of uncompensated bradycardia was observed in 5 of 7 infants diagnosed as dying from SIDS. This was an irreversible situation in spite of resuscitation efforts in 3 of these infants (Poets, Meny, Chobanian, & Bonofiglio, 1999).

Role of the nervous system in regulating blood pressure

Regulation of blood pressure is very complex and is influenced by many physiologic systems including, kidney and heart function, and the central and peripheral nervous systems. Arterial pressure is constantly regulated to maintain tissue perfusion and blood supply. Cardiac output can be changed by signals from receptors in the heart, vessels and peripheral resistance (Henshaw, 2005).

Central nervous system control of blood pressure occurs primarily in the medulla oblongata in the brain stem. Baroreceptors in the aorta and carotid artery send signals through sympathetic pathways via glossopharyngeal and vagal cranial nerves. Catecholamines, epinephrine and norepinephrine, are secreted by the adrenal medulla and enforce sympathetic activity. Additionally, vasopressors control blood pressure by adjusting blood volume. The renin-angiotensin-aldosterone-system (RAAS) is instrumental in regulation of blood pressure. A reduction in renal perfusion stimulates the RAAS, which results in peripheral vascular smooth muscle vasoconstriction. Angiotensin II stimulates aldosterone, which causes shifts in fluids and electrolytes, specifically sodium retention and potassium excretion. Vasopressin (antidiuretic hormone) controls water volume in the circulation and also is a potent peripheral vasoconstrictor (Hazinski & Jenkins, 2002; Lingappa & Farey, 2000a, 2000b; McCance, 2002).

During a stressful event, the primary control is through the sympathetic response, which increases heart rate, vascular contractility and blood pressure in the arterioles through the release of catecholamines from the adrenal medulla. Control of blood pressure is primarily innervated by sympathetic nerves. Inhibition of this control, rather than an increase in parasympathetic tone, is required to change the sympathetic response (Henshaw, 2005).

The parasympathetic system balances sympathetic response primarily through vagal nerve response. Parasympathetic fibers are stimulated by the release of acetylcholine (ACh) from parasympathetic nerves, and have direct vasodilatory action through release of nitric oxide and guanylyl cyclase activation. Acetylcholine release can trigger the release of kallikrein from glandular tissue, which acts upon kininogen to form kinins like bradykinin. Kinins cause increased capillary permeability and venous constriction, along with arterial vasodilation in specific organs. Vagal stimulation also slows heart rate (McCance, 2002)

These two complementary systems maintain homeostatic blood pressure control. Both sympathetic and parasympathetic systems are stimulated by ACh through nicotinic acetylcholine receptors (nAChR) for a primary response in the postganglionic neuron, which

then transmits to muscarinic or adrenergic receptors in the effector cell. Any changes in ACh responsiveness can affect both systems (Lingappa & Farey, 2000a,2000b). Prenatal nicotine exposure is known to cause changes in ACh responsiveness and an increase in parasympathetic tone in neonatal animals (Navarro et al., 1989).

Nicotine

Nicotine is an agonist to the nAChR. In adults, the action of ACh at neuromuscular and preganglionic receptor sites increases sympathetic responses; however, in the developing fetus, continued exposure to nicotine dulls this response and changes autonomic control. Perinatal nicotine exposure in rat pups has been shown to diminish sympathetic responsiveness to hypoxic events. Decreased ability to recover from apneic episodes could be an important cause of SIDS (Slotkin, Lappi, McCook, Lorber, & Seidler, 1995). Inadequate response to shock might work through similar changes in autonomic control. Hypotensive events caused by sepsis and the release of nitric oxide could lead to a lethal shock response as well as respiratory failure.

Activation of nAChR stimulates gamma-aminobutyric acid (GABA) inhibition of cardiac vagal tone in relation to respiration. If these receptors are no longer sensitive, there could be an increase in vagal tone and decreased response to hypotension. In SIDS, the last event before death is sustained bradycardia and apnea. This could be due to increased cardiac vagal tone in response to apnea, hypoxia (Huang et al., 2004; Slotkin, Saleh, McCook, & Seidler, 1997) or hypotension.

Age of Vulnerability

While defects from chronic hypoxia or nicotine exposure during pregnancy are thought to be related to malfunctions in the brainstem, normal developmental changes might have an additive effect on the ability to regulate blood pressure, heart rate and respiration. It has been hypothesized that infants dying of SIDS have a flaw in brainstem regulation; however, normal developmental changes could also be of concern.

Certain infants might be born with chemical defects in the ventral medulla, which is involved in the reflexive regulation of blood pressure and breathing during sleep, and controls the response to low oxygen and high carbon dioxide levels (Kinney et al., 2001). Changes in oxygen and carbon dioxide might be responsible for the increased risk with prone sleeping. Normal infants rouse and turn their heads in response to this challenge. However, SIDS infants appear to have a decreased arousal.

Heat shock might also be involved in the risk of prone sleeping (Guntheroth & Spiers, 2001). SIDS infants might be particularly vulnerable to heat stress, which is most likely to occur when babies are on their stomachs and/or over-swaddled. The main symptom is sweating, but body temperature does not have to rise for the stress to be life-threatening. Guntheroth suggests that problems with re-breathing would rarely cause death but are more likely due to thermal stress (Guntheroth & Spiers, 2001). Heat can also lower blood pressure, additionally stressing the infant.

Conclusion

The idea that shock is a factor in SIDS is not unique (Harper, 2000; Reid, 1998). Reports from parents have often described that their infants were not totally “normal” in the days prior to a SIDS death. It has also been reported that these infants were seen by a primary care practitioner in the days prior to a SIDS death (Rambaud et al., 1999; Willinger, James, & Catz, 1991). Some of these infants have been described as “listless” or “droopy” with increased sweating at the time of death (Kahn et al., 1992; Taylor, Williams, Mitchell, & Ford, 1996). Increased

sweating during infancy is an unusual finding and is indicative of a response to an abnormal event such as heat stress, infection, vasomotor instability or a shock-like state. These are subtle signs that SIDS infants are not normal prior to death and that shock might be involved in the pathophysiology.

It is not clear how humans develop the ability to withstand and compensate for low blood pressure and heart rate, or how the sympathetic and parasympathetic response develops. Whatever the cause of cardiovascular failure, the mechanisms are similar. Infants between 2 and 6 months of age appear to have a vulnerable time point during which they might not be able to respond in a protective way to challenges to cardiac and respiratory function, including response to hypotension. This might result from damage to their autonomic and central nervous system by nicotine, a toxic perinatal exposure or a genetic susceptibility. Then when challenged by stressors from an environmental increase in heat, infection or an increase in nitric oxide release and hypotension from a rapid septic shock event, they are unable to compensate (Figure 1). Given the multifactorial nature of SIDS it is likely that an abnormal response to a cardiovascular event could precipitate death.

References

- American Heart Association. 2005 American Heart Association (AHA) Guidelines for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care (ECC) of Pediatric and Neonatal Patients: Pediatric Basic Life Support. *Pediatrics* 2005;117(5):e989–e1004.
- Beckwith, JB. Discussion of terminology and definition of the sudden infant death syndrome. In: Bergman, AB.; Beck, JB.; Ray, GC., editors. *Sudden Infant Death Syndrome; Proceedings of the Second International Conference on the Causes of Sudden Death in Infants*; University of Washington Press; 1970. p. 14-22.
- Berry PJ. Pathological findings in SIDS. *J Clin Pathol* 1992;45(11 Suppl):11–16. [PubMed: 1474151]
- Blackwell CC, Gordon AE, James VS, MacKenzie DAC, Mogensen-Buchanan M, el Ahmer OR, et al. The role of bacterial toxins in Sudden Infant Death Syndrome (SIDS). *International Journal of Medical Microbiology* 2002;291(6-7):561–570. [PubMed: 11892683]
- Blackwell CC, Moscovis SM, Gordon AE, Al Madani OM, Hall ST, Gleeson M, et al. Ethnicity, infection and sudden infant death syndrome. *FEMS Immunology and Medical Microbiology* 2004;42(1):53–65. [PubMed: 15325398]
- Blackwell CC, Moscovis SM, Gordon AE, Al Madani OM, Hall ST, Gleeson M, et al. Cytokine responses and sudden infant death syndrome: genetic, developmental, and environmental risk factors. *Journal of Leukocyte Biology* 2005;78(6):1242–1254. [PubMed: 16204631]
- Blood-Siegfried J, Nyska A, Geisenhoffer K, Lieder H, Moomaw C, Cobb K, et al. Alteration in regulation of inflammatory response to influenza a virus and endotoxin in suckling rat pups: a potential relationship to sudden infant death syndrome. *FEMS Immunology and Medical Microbiology* 2004;42(1):85–93. [PubMed: 15325401]
- Blood-Siegfried J, Nyska A, Lieder H, Joe M, Vega L, Patterson R, et al. Synergistic effect of influenza a virus on endotoxin-induced mortality in rat pups: a potential model for sudden infant death syndrome. *Pediatric Research* 2002;52(4):481–490. [PubMed: 12357040]
- Blood-Siegfried J, Rambaud C, Nyska A, Germolec D. Evidence for infection, inflammation and shock in sudden infant death: parallels between a neonatal rat model of sudden death and infants who died of SIDS. *Innate Immunity*. (in press).
- Bone RC. Immunologic dissonance: a continuing evolution in our understanding of the systemic inflammatory response syndrome (SIRS) and the multiple organ dysfunction syndrome (MODS). *Annals of Internal Medicine* 1996;125(8):680–687. [PubMed: 8849154]
- Burchell A, Lyall H, Busuttill A, Bell E, Hume R. Glucose metabolism and hypoglycaemia in SIDS. *Journal of Clinical Pathology* 1992;45(11 Suppl):39–45. [PubMed: 1335459]
- Dundar M, Lanyon WG, Connor JM. Scottish frequency of the common G985 mutation in the medium-chain acyl-CoA dehydrogenase (MCAD) gene and the role of MCAD deficiency in sudden infant

- death syndrome (SIDS). *Journal of Inherited Metabolic Disease* 1993;16(6):991–993. [PubMed: 8127075]
- Fifer WP, Myers MM. Sudden fetal and infant deaths: shared characteristics and distinctive features. *Seminars in Perinatology* 2002;26(1):89–96. [PubMed: 11876573]
- Gilbert R, Rudd P, Berry PJ, Fleming PJ, Hall E, White DG, et al. Combined effect of infection and heavy wrapping on the risk of sudden unexpected infant death. *Archives of Disease in Childhood* 1992;67(2):171–177. [PubMed: 1543374]
- Gordon AE, MacKenzie DAC, el Ahmer OR, Al Madani OM, Braun JM, Weir DM, et al. Evidence for a genetic component in Sudden Infant Death Syndrome. *Child Care Health and Development* 2002;28:27–29.
- Gozal D. Deficient heat shock protein expression: a potential mechanism for the sudden infant death syndrome. *Medical Hypotheses* 1996;46(1):52–54. [PubMed: 8746129]
- Guntheroth WG, Spiers PS. Thermal stress in sudden infant death: Is there an ambiguity with the rebreathing hypothesis? *Pediatrics* 2001;107(4):693–698. [PubMed: 11335746]
- Harper RM. Sudden infant death syndrome: a failure of compensatory cerebellar mechanisms? *Pediatric Research* 2000;48(2):140–142. [PubMed: 10926286]
- Harper RM. Autonomic control during sleep and risk for sudden death in infancy. *Archives Italiennes De Biologie* 2001;139(3):185–194. [PubMed: 11330200]
- Harper RM, Kinney HC, Fleming PJ, Thach BT. Sleep influences on homeostatic functions: implications for sudden infant death syndrome. *Respiration Physiology* 2000;119(2-3):123–132. [PubMed: 10722855]
- Harrison LM, Morris JA, Telford DR, Brown SM, Jones K. The nasopharyngeal bacterial flora in infancy: effects of age, gender, season, viral upper respiratory tract infection and sleeping position. *FEMS Immunology and Medical Microbiology* 1999;25(1-2):19–28. [PubMed: 10443488]
- Hazinski, M.; Jenkins, M. Shock, Multiple Organ Dysfunction Syndrome, and Burns in Children. In: McCance, K.; Huether, S., editors. *Pathophysiology: The Biologic Basis for Disease in Adults and Children*. 4th ed. Mosby Inc.; St Louis: 2002. p. 1513-1540.
- Henshaw, C. Alterations in Blood Pressure. In: Copstead, L.; Banasik, J., editors. *Pathophysiology*. WB Saunders; Philadelphia: 2005.
- Hodgman JE, Siassi B. Prolonged QTc as a risk factor for SIDS. *Pediatrics* 1999;103(4 Pt 1):814–815. [PubMed: 10103309]
- Holgate ST, Walters C, Walls AF, Lawrence S, Shell DJ, Variend S, et al. The anaphylaxis hypothesis of sudden infant death syndrome (SIDS): mast cell degranulation in cot death revealed by elevated concentrations of tryptase in serum. *Clinical & Experimental Allergy* 1994;24(12):1115–1122. [PubMed: 7889424]
- Huang ZG, Wang X, Evans C, Gold A, Bouairi E, Mendelowitz D. Prenatal nicotine exposure alters the types of nicotinic receptors that facilitate excitatory inputs to cardiac vagal neurons. *Journal of Neurophysiology* 2004;92(4):2548–2554. [PubMed: 15212427]
- Kahn A, Groswasser J, Rebuffat E, Sottiaux M, Blum D, Foerster M, et al. Sleep and cardiorespiratory characteristics of infant victims of sudden death: a prospective case-control study. *Sleep* 1992;15(4):287–292. [PubMed: 1519001]
- Kinney HC, Filiano JJ, Harper RM. The neuropathology of the sudden infant death syndrome. A review. *Journal of Neuropathology and Experimental Neurology* 1992;51(2):115–126. [PubMed: 1538236]
- Kinney HC, Filiano JJ, White WF. Medullary serotonergic network deficiency in the sudden infant death syndrome: Review of a 15-year study of a single dataset. *Journal of Neuropathology and Experimental Neurology* 2001;60(3):228–247. [PubMed: 11245208]
- Krous HF. Sudden infant death syndrome: pathology and pathophysiology. *Pathology Annals* 1984;19:1–14.
- Lingappa, V.; Farey, K. *Physiological Medicine: A clinical Approach to basic medical physiology*. McGraw-Hill; New York: 2000a. Command Control of Organ Systems; p. 113-153.
- Lingappa, V.; Farey, K. *Physiological Medicine: A clinical Approach to basic medical physiology*. McGraw-Hill; New York: 2000b. Fluid, Electrolyte, Acid-Base and Blood Pressure Regulation; p. 455-510.

- Lundemose JB, Smith H, Sweet C. Cytokine release from human peripheral blood leucocytes incubated with endotoxin with and without prior infection with influenza virus: relevance to the sudden infant death syndrome. *International Journal of Experimental Pathology* 1993;74(3):291–297. [PubMed: 8392861]
- Maron BJ, Clark CE, Goldstein RE, Epstein SE. Potential role of QT interval prolongation in sudden infant death syndrome. *Circulation* 1976;54(3):423–430. [PubMed: 947572]
- McCance, K. Structure and Function of the Cardiovascular and Lymphatic Systems. In: McCance, K.; Huether, S., editors. *Pathophysiology: The Biologic Basis for Disease in Adults and Children*. 4th ed. Mosby Inc.; St Louis: 2002. p. 930-979.
- Molony N, Blackwell CC, Busuttill A. The effect of prone posture on nasal temperature in children in relation to induction of staphylococcal toxins implicated in sudden infant death syndrome. *FEMS Immunology and Medical Microbiology* 1999;25(1-2):109–113. [PubMed: 10443498]
- Morris JA. The common bacterial toxins hypothesis of sudden infant death syndrome. *FEMS Immunology and Medical Microbiology* 1999;25(1-2):11–17. [PubMed: 10443487]
- Morris JA, Haran D, Smith A. Hypothesis: common bacterial toxins are a possible cause of the sudden infant death syndrome. *Medical Hypotheses* 1987;22(2):211–222. [PubMed: 3646461]
- Navarro HA, Seidler FJ, Eylers JP, Baker FE, Dobbins SS, Lappi SE, et al. Effects of prenatal nicotine exposure on development of central and peripheral cholinergic neurotransmitter systems. Evidence for cholinergic trophic influences in developing brain. *Journal of Pharmacology and Experimental Therapeutics* 1989;251(3):894–900. [PubMed: 2600820]
- Platt MS, Yunginger JW, Sekulaperlman A, Irani AMA, Smialek J, Mirchandani HG, et al. Involvement of Mast-Cells in Sudden-Infant-Death-Syndrome. *Journal of Allergy and Clinical Immunology* 1994;94(2):250–256. [PubMed: 8064077]
- Poets CF, Meny RG, Chobanian MR, Bonofiglio RE. Gasping and other cardiorespiratory patterns during sudden infant deaths. *Pediatric Research* 1999;45(3):350–354. [PubMed: 10088653]
- Rambaud C, Guibert M, Briand E, Grangeot-Keros L, Coulomb-L'Hermin A, Dehan M. Microbiology in sudden infant death syndrome (SIDS) and other childhood deaths. *FEMS Immunology and Medical Microbiology* 1999;25(1-2):59–66. [PubMed: 10443492]
- Raza MW, Blackwell CC. Sudden infant death syndrome, virus infections and cytokines. *FEMS Immunology and Medical Microbiology* 1999;25(1-2):85–96. [PubMed: 10443495]
- Raza MW, el Ahmer OR, Ogilvie MM, Blackwell CC, Saadi AT, Elton RA, et al. Infection with respiratory syncytial virus enhances expression of native receptors for non-pilate *Neisseria meningitidis* on HEP-2 cells. *FEMS Immunology and Medical Microbiology* 1999;23(2):115–124. [PubMed: 10076908]
- Reid GM. Sudden infant death syndrome and the modulation of neuropeptides released during shock. *Medical Hypotheses* 1998;51(1):23–26. [PubMed: 9881832]
- Rognum TO, Saugstad OD. Biochemical and immunological studies in SIDS victims. Clues to understanding the death mechanism. *Acta Paediatrica, Supplement* 1993;82(Suppl 389):82–85. [PubMed: 8374202]
- Sawczenko A, Fleming PJ. Thermal stress, sleeping position, and the sudden infant death syndrome. *Sleep* 1996;19(10 Suppl):S267–270. [PubMed: 9085528]
- Schwarz A. Shock. 2006
- Slotkin TA, Lappi SE, McCook EC, Lorber BA, Seidler FJ. Loss of neonatal hypoxia tolerance after prenatal nicotine exposure: implications for sudden infant death syndrome. *Brain Research Bulletin* 1995;38(1):69–75. [PubMed: 7552377]
- Slotkin TA, Saleh JL, McCook EC, Seidler FJ. Impaired cardiac function during postnatal hypoxia in rats exposed to nicotine prenatally: implications for perinatal morbidity and mortality, and for sudden infant death syndrome. *Teratology* 1997;55(3):177–184. [PubMed: 9181671]
- Taylor BJ, Williams SM, Mitchell EA, Ford RP. Symptoms, sweating and reactivity of infants who die of SIDS compared with community controls. New Zealand National Cot Death Study Group. *Journal of Paediatrics and Child Health* 1996;32(4):316–322. [PubMed: 8844537]
- Wedgewood, RJ. Review of USA experience. In: FE, C.; RG, C., editors. *Sudden and Unexplained Deaths in Infancy (Cot Deaths)*. Vol. Vol. 28. Wright; Bristol England: 1972.

Willinger M, James LS, Catz C. Defining the sudden infant death syndrome (SIDS): deliberations of an expert panel convened by the National Institute of Child Health and Human Development. *Pediatric Pathology* 1991;11(5):677–684. [PubMed: 1745639]

Figure 1.

This model shows the relationship between known variables of SIDS and their effect on cardiovascular challenges such as shock. Stressors are conditions that have been shown to lower blood pressure. Vulnerability factors are thought to influence how the infant responds to a cardiovascular challenge. If the infant is unable to respond to the cardio-vascular demand they respond with gasping, bradycardia and eventually death.

Table 1
Factors related to SIDS risk

Comparing the theoretical cause of pathology in 2 common theories of SIDS.

	Common Bacterial	Triple-Risk
Winter and fall.	Season with most infection	More covering with increased hypoxia and hyperthermia
Heat Shock Stress	Increases in bacterial pyrogenic toxin production and fever	Hyperthermia stress
Prone sleeping	<u>Increases bacterial numbers and species in upper airways; Increases temperature to a range permissive for induction of pyrogenic toxins.</u>	Re-breathing of CO ₂ , soft bedding and suffocation
Age 2-6 months	Decrease in protective cortisol production.	Changes in protective autonomic control centers.
Smoking	<u>Increased oxidative stress; enhanced bacterial binding to mucosal cells; increased bacterial load in adult caretakers who smoke; increased viral respiratory infections; reduction in IL-10 response.</u>	Nicotine damage to brain and respiratory center. Impaired respiration with secondary smoke (hypoxia). Changes in autonomic control.
Protective effect of breastfeeding	<u>Reduction of bacterial colonization by antibodies and glycoconjugates in milk; presence of antitoxins in breast milk.</u>	<u>Formula fed infants sleep more deeply and longer than breast fed infants which may interfere with the ability to respond to an adverse event.</u>