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Emergency Medicine Reports

The Practical Journal of Pediatric Emergency Medicine

Volume 9, Number 2 February 2004

Sudden Infant Death Syndrome: What It Is, and What It Is Not

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The death of a child is a terrifying, overwhelming experience for both parents and physicians. The unknown variables and the inability to reverse an etiology make the emergency department (ED) physician feel powerless and unable to give the parents a reason for the event. This article provides a comprehensive update for the ED physician and a review of the truths and myths about the condition known as SIDS.

— The Editor

Introduction

Infants may die suddenly and unexpectedly. The cause of death may be determined, but if it cannot be determined, the term sudden infant death syndrome (SIDS) is applied. SIDS is a diagnosis that is more descriptive than etiologic. Other terms, such as crib death or cot death, also have been used.

Nothing is more devastating to a family than the death of a child. A diagnosis of SIDS compounds the grief with a cascade of events far outside a family's control. It begins with the coroner and police, continues with guilt and sadness, and is sustained by a continued feeling of emptiness and loss. This mysterious and painful process has been the subject of intense study for decades, yet very little is known about this phenomenon. Many hypotheses have been developed; some have shed light, others have increased darkness and delayed understanding.

Within the last decade, it has become clear that SIDS is a syndrome rather than a single disorder and most likely has different causes from one individual to another. Moreover, SIDS and apparent life-threatening events (ALTEs) have been demonstrated to recur in families and, therefore, are suspected of having an autosomal recessive cause in some cases. This is clear, despite the infrequent but documented occurrence of multiple infant deaths within the same families attributable to deliberate abuse, episodes that receive enormous publicity. The cause of death must be ascertained whenever possible for adequate parental counseling, including genetic counseling when applicable.

Definition

SIDS is a term that first was proposed in 1969 for a distinctive subgroup of unexpected infant deaths that occur during the post-

neonatal period with relatively consistent clinical, epidemiological, and pathological features.[1] This term played an important role by focusing attention on a major category of postneonatal infant death, providing support to grieving families, and diminishing the guilt and blame characteristics of these deaths. The 1969 definition was as follows: "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 for death."[1]

Following the development of the 1969 definition, studies demonstrated that a thorough investigation, including a death scene investigation, sometimes will reveal a recognizable and potentially preventable cause of death. In one of these studies, strong evidence of accidental death, most commonly asphyxiation and hyperthermia, was found in almost one-fourth of the cases diagnosed as SIDS.[2]

Although SIDS has several distinctive features, including age distribution and apparent occurrence during sleep, these features were not included in the definition. Because this original definition lacked sufficient explicit criteria, individuals with theories or findings that they believe to be related to SIDS have been able to attach this term to cases that differ drastically from the usual profile.[1] A dramatic illustration of this was a 1972 report of five siblings presumed to have died of SIDS.[3] One of the victims in that family died at 28 months, and another was said to have died while awake and being fed. Postmortem examinations performed in only three of these deaths yielded results "consistent with SIDS." Historic or laboratory evidence suggesting an apneic disorder preceding the death of some of these infants resulted in massive attention directed toward home apnea monitoring as a means of preventing SIDS.[1] Eventually, the five infants in the original report were proved to have been victims of infanticide.[4]

For these and other reasons, an expert panel amended the definition of SIDS to include a review of the case history and an investigation of the death scene. This revised version was published in 1991: "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."[5]

However, despite modifications published in 1991, SIDS remains a diagnosis of exclusion.[1,6,7] As such, SIDS can be distinguished from other infant deaths only by rigorous review of the case by the physician of record and the diagnosing pathologist. The current definition of SIDS leaves the pathologists free to apply this designation either too liberally or too restrictively.[1]

When SIDS is diagnosed too restrictively or not at all, the family often is denied the benefits of a SIDS grief support system. Unwillingness to diagnosis SIDS also can lead to inappropriate suspicion of blame directed toward parents or caregivers, including unfounded self-accusation.

No less unfortunate are some situations in which the SIDS diagnosis has been applied too liberally. Lethal genetic disorders and infanticide have been misdiagnosed as SIDS. Overuse of the diagnosis has contributed to the criticism of the SIDS concept by respected physicians who suggest that SIDS is not a true entity.[1,8,9]

Epidemiology/Pathogenesis

SIDS is the most common cause of death in infants 1-6 months of age.[10] SIDS rarely is seen during the first week of life, and 95% of SIDS deaths occur before 6 months of age. The age-at-death distribution of SIDS is the single most consistent and unique characteristic yet identified. The Back to Sleep campaign has been associated with a substantial reduction in the number of infant deaths in the United States and elsewhere. This reduction primarily has occurred among those infants who composed the most typical SIDS cases in the past. The peak in the age distribution curve between 2 and 4 months has become less prominent.

Pediatric Emergency Medicine Reports™ (ISSN 1082-3344) is published monthly by Thomson American Health Consultants, 3525 Piedmont Road, N.E., Six Piedmont Center, Suite 400, Atlanta, GA 30305. Telephone: (800) 688-2421 or (404) 262-7436.

Vice President/Group Publisher: Brenda Mooney
Editorial Group Head: Valerie Loner
Managing Editor: Allison Mechem
Marketing Manager: Schandale Kornegay

GST Registration No.: R128870672

Periodicals Postage Paid at Atlanta, GA 30304.

POSTMASTER: Send address changes to ***Pediatric Emergency Medicine Reports***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $57.
Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

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Subscription Prices

1 year *with* 30 ACEP, AMA, or AAP Category 1 credits: $389;
1 year without credit: $339;

Multiple copies:
One to nine additional copies: **$305 each;**
10 or more additional copies: **$271 each.**

Resident's Rate: **$169.50**

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Table 1. Risk Factors for SIDS

INFANT

- Prematurity < 37 weeks and < 2500 g
- Intensive neonatal care requirement
- Bronchopulmonary dysplasia
- Previous acute life-threatening event (ALTE)
- Poor weight gain
- Apgar scores < 6 at 5 minutes
- Neonatal respiratory abnormalities
- African-American infants
- Male infants
- Sibling with SIDS
- Obstructive sleep apnea

MATERNAL

- Smoking*
- Maternal age < 20 years
- Alcohol and drug abuse
- Inadequate prenatal care

OTHER

- Prone sleeping position*
- Race
- Socioeconomic status
- Lack of breast feeding*
- Illness recognition
- Soft bedding
- Ethnicity
- Cultural influences
- Co-sleeping
- Unaccustomed prone position

* Important preventable risk factors

Infants now dying suddenly and unexpectedly include a higher proportion of atypical cases.[1]

Virtually all SIDS victims are found dead after being put down to sleep. Ninety percent of deaths occur between midnight and 9 a.m.; the death is silent. Invariably, resuscitation has been attempted by trained parents/relatives, emergency personnel through 911 calls, or individuals at local pediatric offices or EDs. The infants may be found with clenched fists, discharge from the nose or mouth, and mottling.[6]

Other common features include a seasonal distribution (tending to spare the summer months in most years), an association with minor viral infections, prematurity, and social disadvantage. Preterm infants die from SIDS later after birth than their full-term counterparts, yet their corrected post-conceptional age has not reached that of full-term infants.[11] In other words, both immaturity and postnatal experience play a role in deaths from SIDS.

A similar degree of uniformity is apparent in autopsy findings, with most babies having prominent intrathoracic petechiae, pulmonary congestion and edema, minor inflammatory infiltrates usually found in the respiratory tract, and empty bladders.[1] There is no autopsy finding pathognomonic of SIDS and no finding required for the diagnosis.

Neuropathologic studies in SIDS victims support the concept that they are not entirely normal prior to death, but rather possess underlying vulnerabilities that put them at risk for sudden death. This concept forms a key link in a triple-risk model for the pathogenesis of SIDS.[12] According to this model, sudden death in SIDS results from the intersection of three overlapping factors: 1) a vulnerable infant; 2) a critical developmental period in homeostatic control; and 3) an exogenous stressor(s). An infant will die of SIDS only if he/she possesses all three factors; the infant's vulnerability lies latent until he/she enters the critical period and is subject to an exogenous stressor. According to this model, heterogeneous disorders may make the infant vulnerable to sudden death during the critical period, as potentially exemplified by two previously reported lesions in SIDS brains (arcuate nucleus hypoplasia and subtle hypomyelination). Nevertheless, the triple-risk model does not preclude the possibility that the majority of SIDS deaths will be explained by a single common pathway upon which multiple stressors impinge to produce sudden death during the critical period.

The concept of a critical developmental period is based on the consistent age distribution for SIDS. Up to 95% of deaths occur in the first 6 months, with a peak at 2-4 months and a relative sparing of the first month. The triple-risk model addresses this common link by emphasizing the importance of physiologic changes that occur normally during this age range.[13] During this period, major changes occur in virtually all physiologic systems as infants attain adaptive mechanisms enabling them to maintain homeostasis. These changes include dramatic transitions in homeostatic systems regulated by the brain, notably autonomic control, ventilation, sleep-waking organization, temperature regulation, and circadian rhythms.[12] Although changes in cardiopulmonary function and state organization continue throughout life, a relatively stable configuration is achieved by the end of the first 6 months of life. During this same period, the brain undergoes spectacular developmental changes, with an almost doubling of overall weight.[12] Given the complexity, rapidity, and extent in brain growth, and inherent instability in the rapid transitions in homeostatic control, subtle perturbations may be devastating. The concept that an external stressor precipitates sudden death is derived from epidemiologic studies indicating that minor respiratory or gastrointestinal illness occurs around the time of death in the majority of SIDS victims.[12,13] Other potential stressors linked to SIDS are discussed in more detail in the following section.

Several misconceptions exist about what causes SIDS. The syndrome is not caused by a contagious disease or immunization.[7] Neither is it the result of external suffocation, vomiting and choking, or child abuse.[7] It cannot be predicted by apparent life-threatening events.[14] Evidence has revealed certain risk factors or stressors for SIDS, however. *(See Tables 1 and 2.)*

Risk Factors

Prone Sleep Position. Prone (stomach) sleeping has been recognized as a major risk factor for SIDS in various well designed epidemiologic studies.[10,15] The plausibility of a casual association between prone sleep positioning and SIDS is made most compelling by the observation that in countries in which campaigns to reduce the prevalence of prone sleeping have been

Table 2. Environmental Factors and SIDS Risk

FACTORS IN SLEEPING ENVIRONMENT	ODDS RATIO (95% CONF)
Prone sleeping	10.0 (4.3-23.2)
Side sleeping	2.2 (1.4-3.4)
Covers over infant's head	31.4 (10.4-95.0)
Wearing hat	6.2 (0.7-51.9)
Heating on all night	3.1 (1.6-6.2)
If mother ever breast-fed	0.4 (0.3-0.7)
Bedsharing with parents all night	4.1 (1.8-9.2)
Using pacifier	0.4 (0.3-0.7)
Using duvet (quilt)	1.9 (1.1-3.1)
Loose bed coverings	1.3 (0.8-2.0)
Maternal smoking during pregnancy	4.8 (3.3-7.0)
Paternal smoking after pregnancy	2.9 (1.6-5.3)
Infant exposure to cigarette smoke:	
1-2 hours/day	2.0 (1.2-3.4)
3-5 hours/day	3.4 (1.9-6.1)
6-8 hours/day	7.3 (3.5-15.5)
> 8 hours/day	9.5 (5.2-17.4)

successful (including the United States), dramatic decreases in the SIDS rates have occurred. The association further is strengthened by observations that in cultures in which prone sleeping is rare, SIDS rates historically have been very low.[16]

The original 1992 sleeping position recommendation from the American Academy of Pediatrics (AAP) identified any nonprone position (i.e., side or supine) as being optimum for reducing SIDS risk.[17] Subsequent studies have shown that side-sleeping has a higher risk than the supine position, although the side-sleeping position still seems to be considerably safer than prone.[18] The higher risk for SIDS among infants placed on their sides may relate to the relative instability of this position. Although infants placed on their sides usually roll to their backs, the risk of rolling to the prone position from the side is significantly greater than rolling to the prone position from the back.[19]

The AAP, the national Back to Sleep campaign, and the U.S. Public Health Service currently emphasize using the supine sleep position for infants rather than any other nonprone position, and the Healthy People 2010 objectives set a target goal of having 70% of all infants sleeping on their backs by the year 2010.[18]

The rate of SIDS among African-Americans is the highest and continues to be greater than twice that among white infants (1.30 vs. 0.56 per 1000 live births),[18] and national data consistently show an association between African-American race/ethnicity and use of the prone sleep position.[19-23] Other risk factors for the prone position include multiparity, maternal Hispanic race/ethnicity, young age, low education, poverty, public insurance, being unmarried, and having a grandmother living at home.[18-23] Some studies have shown that certain maternal health behaviors, including late prenatal care and limited breast-feeding, also are associated with the prone sleep position.[18,24]

Many families who choose the prone sleep position cite increased infant comfort and improved sleeping, despite knowledge of the recommendation to avoid the position.[21] In addition, nearly 20% of caregivers switch from placing infants in the nonprone to the prone sleep position between 1 and 3 months of age, the peak age range for SIDS.[10,22,25]

Physicians must play an active, ongoing role in discouraging prone sleeping. Because the incidence of prone sleeping increases during the first 6 months of life, parents should have the Back to Sleep message consistently reinforced during all health care encounters, beginning as early as possible and continuing throughout the half year. The message should be tailored to anticipate that certain ethnic and sociodemographic groups may rely more on personal experience and perception than on health care provider advice and medical reports of medical advances. Parents are more likely to place their infants in the prone position if they perceive that the infant is happier or sleeps better, despite medical advice to the contrary. Health care providers should acknowledge that prone sleeping infants tend to sleep better, but should caution parents that this sound sleeping may be precisely what puts some infants at higher risk for SIDS.[26] Parents should be counseled to try alternative methods of decreasing sleep arousals, such as swaddling, but care must be taken not to over-bundle infants. It is especially important to target parents with limited social support and those with temperamentally difficult infants.

Also, although parents may know of the recommendation, many other child caregivers, such as day child care center workers, do not.[27,28] Many states have passed regulations requiring nonprone sleep position for infants in child care centers.

More recently, attention has been paid to the issue of unaccustomed prone sleeping.[12,29,30] "Unaccustomed prone" refers to infants who usually were placed nonprone for sleep, but were placed prone for the last sleep. Infants unaccustomed to the prone sleep position are at much greater risk for SIDS when placed prone than if they had been used to prone sleeping.[29-31]

Studies have suggested that the deaths of infants in this circumstance are likely to have been caused by asphyxia as a result of rebreathing of expired air and/or airway obstruction.[29] If so, one can ask why these infants failed to lift and turn their heads to the side — the normal response of an infant whose breathing is compromised when sleeping prone in the face-down position. Two possibilities can be suggested. First, infants who normally sleep supine have later attainment of gross motor skills, including ability to lift their heads, compared with prone-sleeping infants, a situation that also seems to be true for side-sleeping infants.[32] Additionally, although head lifting is a component of the innate startle reflex, to gain access to fresh air, an infant whose face is turned down into the bedding must combine head lifting with head turning. Some normal infants fail to successfully perform this maneuver when placed face down, or do so only after repeated unsuccessful attempts.[29] Such difficulties with airway defense may be the result of the normal developmental dis-

appearance of the startle reflex and other subcortically mediated protective reflexes during the first six months of life. Infants who sleep prone, unlike back- or side-sleepers, normally lift and turn their heads from one side to the other frequently. Lack of practice in employing such head lifting and turning movements could reduce the airway defensive capability in the infant who is inexperienced at prone sleeping and who encounters respiratory difficulty when he or she first manages to get into a prone, face-down position.

Parents must discuss nonprone sleep position with any caretakers for their infants, whether these be relatives, child care providers, or occasional babysitters. It must be emphasized that nonprone sleepers may be at greater risk if ever placed prone. In addition, further efforts to educate child care providers must be ongoing.

Many theories exist as to why supine sleeping reduces the risk of SIDS.[7,26,33-38] Some of the potential problems with the prone sleeping position are listed in Table 3. In the prone sleep position, there is less flexibility in heart-rate variability, reduced vasomotor tone, reduced arousal and waking ability, poorer ventilatory and airway protective responses, and perhaps decreased mechanical efficiency of the diaphragm. All of these occur within the context of the prone position, increasing the exposure to a respiratory stress (rebreathing, airway obstruction, and/or pooling of airways secretions) and promoting peripheral vasodilatation by restricting heat loss. None of these conclusively indicate a direct mechanism of SIDS. However, keeping in mind that SIDS is probably not a single entity, any of these factors alone or in combination could result in a suboptimal physiological response to a life-threatening challenge that would be likely to occur because of the physically compromising features of being prone.

One of the concerns that was raised when recommendations were made to place infants on their backs to sleep to reduce their risk of SIDS was that the number of cases of significant gastric aspiration might increase. Multiple studies have not shown any increase in the rate of choking or aspiration in the supine position.[7,39]

The pattern of early motor development is affected by sleep position. Prone sleepers attain several motor milestones earlier than supine sleepers.[40] However, both groups of infants achieve all milestones within the accepted normal age range.

After the introduction of the Back to Sleep program for the prevention of SIDS, evaluation of the misshapen head has become a very common referral problem for pediatric neurosurgeons.[41,42] The vast majority of these represent positional plagiocephaly — flattening of the occipital region produced by chronic pressure effects on the calvarium in infants who lie supine. Because the cranial sutures remain open in this entity, nonsurgical management generally is highly effective. This includes positional alteration, physical therapy if any underlying torticollis is present, and the application of a cranial orthosis (remolding helmet) in more severely affected cases. Reassurance can be offered that the cosmetic deformity will correct (albeit incompletely) over the course of time, and will not interfere with the normal growth and development of the brain. This realization, in and of itself, is powerful medicine to many families.

Table 3. What Is Wrong with the Prone Sleeping Position?

- Rebreathing of exhaled gas
- Overheating/hyperthermia
- Positional asphyxia (airway obstruction)
- Altered organization of sleep
- Vertebral artery compression
- Reduced responses to environmental stimuli
- Reduced vasomotor tone
- Laryngeal chemoreflex
- Impaired diaphragm strength
- Poorer ventilatory response to mild asphyxia
- Impaired arousability

The pediatrician or other primary care clinician should educate parents as well as other health care professionals, such as those in newborn care units, on methods to decrease the risk of development of deformational plagiocephaly. A certain amount of prone positioning, or "tummy time," while the infant is awake and being observed is recommended to help prevent the development of flat spots on the occiput and to facilitate development of upper shoulder girdle strength necessary for timely attainment of certain motor milestones.[10] Beginning at birth, most deformational plagiocephaly also can be prevented by nightly alternating the supine head position (i.e., left and right occiputs) during sleep and periodically changing the orientation of the infant to outside activity such as is likely to occur at the door of the room.

Maternal Smoking. A large number of epidemiologic studies have documented that smoking during pregnancy and after birth are two major and independent risk factors for SIDS.[43] With the reduction in the incidence of infants being put to sleep prone, maternal smoking has become the major modifiable risk factor for SIDS.[44] It has been argued that 30% of deaths from SIDS are preventable by not exposing infants to cigarette smoke.[45]

The effect of smoke exposure on SIDS risk is dose dependent; the more an infant is exposed to smoke, the higher the risk.[7] Smoking 1-9 cigarettes per day in pregnancy increases the risk more than four times; 10-19 cigarettes per day increases the risk more than five times, and more than 20 cigarettes per day is associated with an eight-fold increase.[46]

Exposure of babies to tobacco smoke from other members of the household before and after birth also increases the risk of death: the greater the exposure, the higher the risk. For every hour of the day that babies habitually spend in a room in which people smoked, the risk of SIDS increased by almost 100%.[46] The risk to babies who spend more than eight hours a day in such a room is more than eight times that of babies who are not exposed to tobacco smoke.

In spite of much effort by investigators around the world, the reason why infants exposed to cigarette smoke have an increased

risk of SIDS is unknown.[47] As yet, no mechanism that explains the final pathway of SIDS has been identified; however, a number of studies have implicated impairment in arousability.[44] Arousal from sleep is an important survival response to a life-threatening event such as hypotension or prolonged apnea.[48] It results in increased heart rate, blood pressure, and ventilation, and a behavioral response is evoked allowing movement away from a potentially harmful stimulus.[44,49] Studies have shown that arousal from both quiet sleep and active sleep is impaired when infants sleep in the prone position.[26,44] Recent studies have shown that maternal tobacco smoking significantly impairs both stimulus-induced and spontaneous arousal from quiet sleep when infants are sleeping in the supine position.[44,45,50,51] This effect is strongest at the age when SIDS incidence is highest.[44] Any impairment in arousability from sleep that compromised ventilation or cardiovascular responses to hypoxia or asphyxia could contribute to the final pathway to SIDS.

The effects of maternal smoking during pregnancy on cardiorespiratory development and function before and after birth are poorly understood. Nicotine, the major constituent of cigarette smoke, readily crosses the placenta and has been found in fetal cord serum in concentrations generally 15% higher than those in maternal serum.[52] Reductions in uterine blood flow of 30-40% have been reported, depending on the dose of nicotine, and this in turn reduces the supply of oxygen and nutrients to the growing fetus.[52] Infants of smoking mothers also have been reported to have raised levels of carboxyhemoglobin.[44] The combination of decreased oxygen delivery and decreased oxygen carrying capacity of the fetal hemoglobin may expose the fetus to hypoxia during uterine life, which in turn has the potential to adversely affect sympathetic activity, cardiovascular control, and fetal growth.[44]

There is now, however, substantial evidence that damage to the developing fetal brain also may be due to the direct toxic effects of nicotine, and that the effects of maternal smoking on later neurological outcome may not all be secondary to hypoxia-ischemia.[52] Nicotine interacts directly with endogenous nicotinic acetylcholine receptors in the brain and profoundly can affect central nervous system function and development; it has been shown that [3H] nicotine-binding sites are heavily concentrated in the tegmental nuclei of the brain, which are involved with cardiopulmonary integration, somatic motor control, and arousal.[53-55]

Maternal smoking also has been demonstrated to adversely affect lung development and function.[56-58] Through alterations in lung mechanics, smoke-exposed infants are likely to become fatigued, and together with poor ventilation-perfusion matching, be subject to respiratory and cardiac failure.[56]

Sleeping Location. Many parents ask about whether it is safe to take their babies to bed with them. Research in this area has been conflicting, with some studies identifying bedsharing as a risk factor for SIDS, while others acknowledge the beneficial effects of close contact between babies and their caregivers and the low SIDS rates in cultures, particularly Asian communities, in which mothers traditionally sleep very close to their babies, often in the same bed.[46,59-61] At 3 months of age, the strongest predictors for bedsharing are being of black or Asian race or ethnicity, followed by being breastfed, having a mother younger than 18 years or unmarried, and low household income.[59]

Recent research has shown that bedsharing for the whole night is associated with an increased risk only if the mother is a smoker or has consumed alcohol or other drugs of abuse.[62] The vast majority of bedsharing mothers whose baby died of SIDS were smokers (86.2%) and the associated risk to infants of these mothers was extremely high, while being nonsignificant among infants of non-smoking mothers.[46] Furthermore, in New Zealand and the United Kingdom, sharing a room with a parent was shown to have a protective effect against SIDS.[46] Recent studies have emphasized the potential hazard of adults sleeping on a sofa or couch with a baby.[60] Advice such as "All babies should be returned to their cots after breastfeeding" errs on the side of caution, and further study is required before such a statement could or could not be made a definitive one. Current advice to parents who wish to bedshare should include statements such as:

- Don't bedshare if you are a smoker;
- Don't bedshare if you or your partner consume alcohol prior to sleep;
- Don't bedshare if you sometimes take illegal drugs; and
- Don't sleep with your baby on a sofa.

There is no published evidence of any increased risk to a baby from sharing a bed with a firm mattress with parents who do not smoke and have not consumed alcohol or other drugs, provided the bedding is arranged so that it cannot slip over the baby's head, and the baby is not sleeping on a pillow or under an adult duvet.

Soft Sleep Surfaces and Loose Bedding. Polystyrene bead-filled pillows were among the first soft sleep surfaces identified as contributing to the deaths of young infants and subsequently were removed from the market following action by the U.S. Consumer Product Safety Commission.[10] Additional epidemiologic studies identified other soft surfaces, such pillows, quilts, comforters, sheepskins, and porous mattresses, as a significant risk factor, particularly when placed under the sleeping infant.[10,15,63,64] A recent study demonstrated that a high-risk group of largely African-American infants sleep on bedding that is softer and have a greater propensity to limit CO_2 dispersed and therefore increases rebreathing.[65] In addition, their parents less often were aware of the risk associated with prone sleeping.

Several reports described that in a significant number of SIDS cases, the heads of the infants, including some infants who slept supine, were covered by loose bedding. Many of these studies found loose bedding to be an epidemiologic risk factor for SIDS.[10,15,66] Physiological studies indicate that facial obstruction by soft bedding may lead to complete airway obstruction, and/or hyperthermia, and/or accidental suffocation by rebreathing.[64] Parents should be advised to place the baby in a "feet-to-foot" position, in which the baby's feet are at the foot of the bed, and bedding is tucked securely in at the bottom of the bed to reduce

the risk of bedding slipping over the baby's head.[46] Parents also should be advised that their infants do not need to wear hats during sleep.[46]

Overheating. There is some evidence that the risk of SIDS is associated with the amount of clothing or blankets on an infant, the room temperature, and the season of the year.[10] The increased risk associated with overheating is particularly evident when infants sleep prone but is less clear when they sleep supine. It is unclear whether the relationship to clothing and climate is an independent factor or merely a reflection of the use of more clothing, quilts, and other potentially asphyxiating objects in the sleeping environment during cold weather. Studies have shown that a mild increase in environmental temperature may adversely affect breathing patterns among both preterm and term infants.[67] Both central and obstructive apnea episodes were increased in duration and rate during environmental hyperthermic conditions.

The SIDS statistics always have shown a distinct seasonality, with higher rates recorded during winter months. It may be that the seasonality reflects increased infections, which also are known to be more frequent during cold weather. A significant decrease has been observed in the seasonal association of SIDS, as prone sleeping has decreased and SIDS rates have decreased, thus suggesting an interaction among environmental factors.[10]

Illness. Having features of illness requiring professional advice is associated with increased risk, although three-quarters of infants who died of SIDS had only minor symptoms or signs, or none at all, prior to their death.[46]

Interventions such as parental education in early illness detection may also have the potential to help reduce the incidence of SIDS. Thornton and colleagues[68] developed the Baby Check Score Card, which consists of a graded checklist of signs and symptoms creating a score on which action to seek medical help or treatment can be based. The potential value of this scoring system has been supported by a study which showed that a significant number of infants who died of SIDS would have been identified as potentially seriously ill by using the Baby Check Score Card.[69]

A high Baby Check score or a history of an apparent life-threatening event is an acute factor which may signify transient increased risk and alert the family and health care professionals caring for the baby to the need for close observation or possible treatment.

Obstructive Sleep Apnea. A strong history of SIDS, ALTEs, and obstructive sleep apnea (OSA) in family members predisposes an infant to have OSA during the first year of life.[70,71] The potential link among SIDS, ALTEs, and OSA in infants is unclear; however, an increased incidence of OSA in subsequent siblings of SIDS and infants with ALTE has been described.[71] In addition, studies have documented obstructive events during sleep in infants who subsequently became victims of SIDS.[71-73] These findings suggest that SIDS and ALTEs are related to OSA. Sleep studies should be obtained in young infants with multiple family histories of SIDS, ALTEs, and OSA.

Table 4. Metabolic Disorders Associated with Sudden Death

- Lactic acidemias
- Aminoacidopathies, organic acidurias
- Glycogen storage diseases
- Carnitine deficiencies/disorders of fatty acid oxidation
- Mitochondrial matrix enzyme defects
  - Acyl-CoA dehydrogenase defects
- Multiple acyl-CoA-dehydrogenase defects
  - Electron transfer flavoprotein (ETF) subunit deficiency

Causes of Infant Death Mistaken for SIDS

Metabolic Disorders. Metabolic disorders associated with sudden death (not SIDS) are listed in Table 4. When more than one infant in a family has died suddenly and unexpectedly, a metabolic disorder or child abuse should be suspected.

The only genetic metabolic disorder clearly linked to sudden unexpected death is medium-chain acylcoenzyme A dehydrogenase (MCAD) deficiency.[74,75] Approximately 5% of all cases of sudden infant death are likely caused by a disorder of fatty acid oxidation.[74] Identification of these patients is important; if ascertained before the onset of treatment, most if not all harmful effects can be treated. In 2000, four states (Maine, Massachusetts, North Carolina, and Wisconsin) screened for MCAD deficitency as part of newborn screening.[76]

Until widespread screening is available, physicians must insist on the following guideline: Do a comprehensive autopsy on all infants who die of SIDS, freeze at least liver and bile specimens, and study further the children with fatty infiltration of liver and other risk factors for metabolic disorders. Because all known disorders of fatty acid oxidation are inherited in an autosomal recessive manner with a 25% recurrence rate, it is common to discover siblings who are affected but clinically free of symptoms once a diagnosis is made in an index case.[74]

Infanticide. The large majority of SIDS cases have no evidence of parental psychiatric disease or neglect of the infant. However, recent publications have documented that a few mothers of infants with a history of ALTEs have been observed trying to harm their infants,[10,77] and several cases previously thought to be multiple cases of SIDS within a family actually were cases of multiple homicide.[4] As the number of cases of true SIDS has decreased in recent years, the proportion of cases attributable to infanticide may be increasing.[8] Estimates of the incidence of infanticide among cases designated as SIDS have ranged from less than 1% to as much as 10%.[10,77-79] A thorough investigation of the case and scene is critical in every case because it improves the chances for an accurate diagnosis.[10,79] When two infants in the same family reportedly have died of SIDS, immediate concern should be raised about the cause of the deaths.

It is impossible to distinguish at autopsy between SIDS and accidental or deliberate asphyxiation with a soft object.[77,79] However, certain circumstances should indicate the possibility of intentional suffocation, including:

• previous recurrent cyanosis, apnea, or ALTE while in the care of the same person;

• age at death older than 6 months;

• previous unexpected or unexplained deaths of one or more siblings;

• simultaneous or nearly simultaneous death of twins;

• previous death of infants under the care of the same unrelated person; or

• discovery of blood on the infant's nose or mouth in association with an ALTE.

Between 1988 and 1998, postneonatal mentality attributable to mechanical suffocation increased among all infants regardless of race and region except for infants residing in the West.[80] This increase reflects a diagnostic shift away from SIDS, stemming from the publication of a stricter case definition of SIDS in 1991 followed by more extensive evaluations of sudden infant deaths, including death scene investigations, in a growing number of states.

Cardiac Arrhythmias. A recent publication reported that a significant number of SIDS cases in Italy had prolongation of the QT interval on a screening electrocardiogram, which may have led to a fatal cardiac arrhythmia.[81] However, questions about the study methods have been raised,[82-89] and it is unlikely that this abnormality will explain more than a small percentage of SIDS cases.[90]

Although mass electrocardiographic screening of newborns may allow early detection of infants with QT prolongation and other cardiac conduction abnormalities, it raises concerns regarding clinical accuracy, physician resources, cost-effectiveness, and parental anxiety.[91,92] Screening for these disorders may be accomplished through careful review of history, physical examination and family health history, as well as selective use of diagnostic testing. Further comprehension of the genetic basis of inherited arrhythmia disorders may help elucidate the mechanisms of arrhythmogenesis and etiologies of sudden infant death.

Management of Sudden, Unexpected Infant Death

Most sudden infant deaths occur at home. Parents are shocked, bewildered, and distressed. The appropriate professional response to any child death must be compassionate, empathic, supportive, and nonaccusatory. Inadvertent comments, as well as necessary questioning by medical personnel and investigators, are likely to cause additional stress. It is important for those in contact with parents during this time to be supportive while at the same time conducting a thorough investigation.

Personnel on first-response teams should be trained to make observations at the scene, including position of the infant, marks on the body, body temperature and rigor, type of bed or crib and any defects, amount and position of clothing and bedding, room temperature, type of ventilation and heating, and reaction of the caregivers. Guidelines are available for death scene investigation of sudden, unexplained infant deaths.[79] Paramedics and ED personnel should be trained to distinguish normal findings, such as postmortem anal dilation and lividity, from trauma attributable to abuse.

When a previous healthy infant has died unexpectedly in the absence of external evidence of injury, a preliminary diagnosis of "probable SIDS" can be given. To the family of a true victim of SIDS, this diagnosis conveys the health care provider's initial impression that they could not have prevented their infant's death. Assignment of this preliminary diagnosis should not limit or prevent subsequent thorough case investigation.

Parents should be informed that other causes of death will be excluded only by thorough death scene investigation, postmortem examination, and review of case records. It should be explained to parents that these procedures might enable them and their physician to understand why their infant died and how other children in the family, including children born later, might be affected. Only on completion of a thorough and negative case investigation (including performance of a complete autopsy, examination of the death scene, and review of the clinical history) should a definitive diagnosis of SIDS be assigned as the cause of death.

The family is entitled to an opportunity to see and hold the infant once death has been pronounced. A protocol may help in planning how and when to address the many issues that require attention, including baptism, grief counseling, funeral arrangements and religious support, cessation of breastfeeding, and the reactions of surviving siblings.[79] All parents should be provided with information about SIDS and the telephone number of the local SIDS support group.

Recommendations to Reduce the Risk of SIDS

During the past decade, a variety of strategies have been developed to reduce the risk of SIDS. The following list is taken from the recommendations by the AAP.[10] (It should be emphasized that the recommendations are intended for sleeping infants and primarily for well infants. Individual medical conditions may warrant a physician to recommend otherwise, after weighing the relative risks and benefits.)

1) Infants should be placed for sleep in a nonprone position. Supine (wholly on the back) confers the lowest risk and is preferred. However, while side sleeping is not as safe as supine, it also has a significantly lower risk than prone.

2) A crib that conforms to the safety standards of the Consumer Product Safety Commission and ASTM International (formerly the American Society for Testing and Materials) is a desirable sleeping environment for infants.

3) Infants should not be put to sleep on waterbeds, sofas, soft mattresses, or other soft surfaces.

4) Avoid soft materials in the infant's sleeping environment.

- Soft objects (such as pillows, quilts, comforters, and sheepskins) should not be placed under a sleeping infant.
- Soft objects (such as pillows, quilts, comforters,

sheepskins, stuffed toys, and other gas-trapping objects) should be kept out of an infant's sleeping environment. Also, loose bedding, such as blankets and sheets, may be hazardous. If blankets are to be used, they should be tucked in around the crib mattress so the infant's face is less likely to become covered by bedding. One strategy is to make up the bedding so that the infant's feet are able to reach the foot of the crib (feet to foot), with the blankets tucked in around the crib mattress and reaching only to the level of the infant's chest. Another strategy is to use sleep clothing with no other covering over the infant.

5) Bedsharing or co-sleeping may be hazardous under certain conditions.

- As an alternative to bedsharing, parents might consider placing the infant's crib near their bed to allow for more convenient breastfeeding and parental contact.
- If a mother chooses to have her infant sleep in her bed to breastfeed, care should be taken to observe the aforementioned recommendations (nonprone sleep position, avoidance of soft surfaces or loose covers, and avoidance of entrapment by moving the bed away from the wall and other furniture and avoiding beds that present entrapment possibilities).
- Adults (other than the parents), children, or other siblings should avoid bedsharing with an infant.
- Parents who choose to bedshare with their infant should not smoke or use substances, such as alcohol or drugs, that may impair arousal.

6) Overheating should be avoided. The infant should be lightly clothed for sleep, and the bedroom temperature should be kept comfortable for a lightly clothed adult. Overbundling should be avoided, and the infant should not feel hot to the touch.

7) A certain amount of tummy time while the infant is awake and observed is recommended for developmental reasons and to help prevent flat spots on the occiput. Positional plagiocephaly also can be avoided by altering the supine head position during sleep. Techniques for accomplishing this include placing the infant to sleep with the head to one side for a week or so and then changing to the other and periodically changing the orientation of the infant to outside activity (e.g., the door of the room).

8) Although various devices have been developed to maintain sleep position or to reduce the risk of rebreathing, such devices are not recommended, because none have been tested sufficiently to show efficacy or safety.

9) Electronic respiratory and cardiac monitors are available to detect cardiorespiratory arrest and may be of value for home monitoring of selected infants who are deemed to have extreme cardiorespiratory instability. However, there is no evidence that home monitoring with such monitors decreases the incidence of SIDS. Prevention of SIDS is not an acceptable indication for home cardiorespiratory monitoring.[93]

There are groups of infants for whom use of a home cardiorespiratory monitor may be warranted, not because of an increased risk of SIDS, but because of other factors that increase the risk of sudden death.[93] Home cardiorespiratory monitoring may be warranted for infants who are technology dependent (tracheostomy, continuous positive airway pressure), have unstable airways, have rare medical conditions affecting regulation of breathing, or have symptomatic chronic lung disease.

10) There is concern that the annual rate of SIDS, which has been decreasing steadily since 1992, now appears to be leveling off, as has the percentage of infants sleeping prone. The Back to Sleep campaign should continue and be expanded to emphasize the safe characteristics of the sleeping environment, including safe bedding practices, and focus on the portion of the population that continues to place their infants prone. Other potentially modifiable risk factors, such as avoidance of maternal smoking, overheating, and certain forms of bedsharing, should be included as important secondary messages.

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CME Objectives

The CME objectives for *Pediatric Emergency Medicine Reports* are to help physicians:

a.) Quickly recognize or increase index of suspicion for specific conditions;

b.) Understand the epidemiology, etiology, pathophysiology, historical and physical examination findings associated with the entity discussed;

c.) Be educated about how to correctly formulate a differential diagnosis and perform necessary diagnostic tests;

d.) Apply state-of-the-art therapeutic techniques (including the implications of pharmacologic therapy discussed) to patients with the particular medical problems discussed;

e.) Provide patients with any necessary discharge instructions.

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Physician CME Questions

11. Which one of the following has been shown to be associated with an increased risk of SIDS?
    A. Anemia
    B. Infant born postterm
    C. Maternal smoking
    D. Recent immunization
    E. Supine sleeping position

12. Which of the following is *not* an indication for the use of a home cardiorespiratory monitor?
    A. Prior ALTE
    B. Prevention of SIDS
    C. Neurologic disorders affecting respiratory control
    D. Tracheostomies

13. Generally accepted risk factors for SIDS include all of the following maternal factors *except:*
    A. cigarette smoking during pregnancy.
    B. low educational level.
    C. young age (< 20 years).
    D. venereal disease during pregnancy.

14. Which one(s) of the following concepts should be explained to the parents of a true SIDS victim by their pediatrician?
    A. Other causes of death will be excluded only by thorough investigation.
    B. The etiology generally is due to an unrecognized abnormality of the central nervous system.
    C. Subsequently born infants should be on home monitors for at least six months.
    D. A risk profile of subsequently born infants can be assessed by use of polysomnography.

15. Generally accepted risk factors for SIDS include all of the following *except:*
    A. low birth weight (< 2500 g).
    B. prematurity (< 37 weeks).
    C. being the larger infant of twins.
    D. African-American race.

16. Of the following, the best statement concerning the currently considered pathogenesis of SIDS is:
    A. The presence of abnormal forms of surfactant initiates progressive alveolar collapse with resultant hypoxemia.
    B. An underlying lower respiratory tract infection triggers periods of prolonged apnea.
    C. Hypoglycemia due to metabolic defects triggers cardiac arrhythmias and subsequent arrest.
    D. Infants who are physically vulnerable may die of SIDS when placed in a risky situation. A prone sleeping position, soft bedding, smoke exposure, and overheating are all risk factors.

17. Which of the following statements regarding SIDS is true?
    A. There is no seasonal distribution in the incidence of SIDS.
    B. Prematurity creates no additional risk of SIDS.
    C. Soft sleep surfaces increase the risk of SIDS.
    D. The Back to Sleep campaign has had no effect on the incidence of SIDS.

18. All of the following statements concerning bedsharing between infants and family members are true *except:*
    A. The adult bed is a common place for the infant to sleep at night.
    B. There are strong cultural influences on the practice of bedsharing.
    C. Bedsharing creates a risk of SIDS if the mother has consumed alcohol or drugs of abuse.
    D. Maternal smoking does not increase the risk of SIDS associated with bedsharing.

19. What is the only genetic disorder associated with sudden infant death?
    A. Medium-chain acylcoenzyme A dehydrogenase deficiency (MCAD)
    B. Down Syndrome
    C. Hirschprung's disease
    D. Cystic fibrosis
    E. Adrenal insufficiency

20. Which of the following suggest(s) the possibility of intentional suffocation?
    A. Previous recurrent cyanosis, apnea, or ALTE while in the care of the same person
    B. Age older than 6 months
    C. Previous unexpected deaths in siblings
    D. Simultaneous death of twins
    E. All of the above

Answer Key

11. C	15. C	19. A
12. B	16. D	20. E
13. D	17. C	
14. A	18. D	

In Future Issues: **Evaluating the Limping Child**

PEDIATRIC Emergency Medicine Reports

The Practical Journal of Pediatric Emergency Medicine

SIDS

Risk Factors for SIDS

INFANT

- Prematurity < 37 weeks and < 2500 g
- Intensive neonatal care requirement
- Bronchopulmonary dysplasia
- Previous acute life-threatening event (ALTE)
- Poor weight gain
- Apgar scores < 6 at 5 minutes
- Neonatal respiratory abnormalities
- African-American infants
- Male infants
- Sibling with SIDS
- Obstructive sleep apnea

MATERNAL

- Smoking*
- Maternal age < 20 years
- Alcohol and drug abuse
- Inadequate prenatal care

OTHER

- Prone sleeping position*
- Race
- Socioeconomic status
- Lack of breast feeding*
- Illness recognition
- Soft bedding
- Ethnicity
- Cultural influences
- Co-sleeping
- Unaccustomed prone position

* Important preventable risk factors

Metabolic Disorders Associated with Sudden Death

- Lactic acidemias
- Aminoacidopathies, organic acidurias
- Glycogen storage diseases
- Carnitine deficiencies/disorders of fatty acid oxidation
- Mitochondrial matrix enzyme defects
  - Acyl-CoA dehydrogenase defects
- Multiple acyl-CoA-dehydrogenase defects
  - Electron transfer flavoprotein (ETF) subunit deficiency

Environmental Factors and SIDS Risk

FACTORS IN SLEEPING ENVIRONMENT	ODDS RATIO (95% CONF)
Prone sleeping	10.0 (4.3-23.2)
Side sleeping	2.2 (1.4-3.4)
Covers over infant's head	31.4 (10.4-95.0)
Wearing hat	6.2 (0.7-51.9)
Heating on all night	3.1 (1.6-6.2)
If mother ever breast-fed	0.4 (0.3-0.7)
Bedsharing with parents all night	4.1 (1.8-9.2)
Using pacifier	0.4 (0.3-0.7)
Using duvet (quilt)	1.9 (1.1-3.1)
Loose bed coverings	1.3 (0.8-2.0)
Maternal smoking during pregnancy	4.8 (3.3-7.0)
Paternal smoking after pregnancy	2.9 (1.6-5.3)
Infant exposure to cigarette smoke:	
1-2 hours/day	2.0 (1.2-3.4)
3-5 hours/day	3.4 (1.9-6.1)
6-8 hours/day	7.3 (3.5-15.5)
> 8 hours/day	9.5 (5.2-17.4)

What Is Wrong with the Prone Sleeping Position?

- Rebreathing of exhaled gas
- Overheating/hyperthermia
- Positional asphyxia (airway obstruction)
- Altered organization of sleep
- Vertebral artery compression
- Reduced responses to environmental stimuli
- Reduced vasomotor tone
- Laryngeal chemoreflex
- Impaired diaphragm strength
- Poorer ventilatory response to mild asphyxia
- Impaired arousability

Supplement to *Pediatric Emergency Medicine Reports*, February 2004: "Sudden Infant Death Syndrome: What It Is, and What It Is Not." *Author:* **Ronald M. Perkin, MD, MA,** Professor and Chairman, Department of Pediatrics, Brody School of Medicine, East Carolina University; Medical Director, Children's Hospital, University Health Systems of Eastern Carolina; Attending Physician, Pediatric Critical Care and Sleep Disorders Center. *Peer Reviewer:* **Roy Vega, MD, FAAP,** Attending Physician, Department of Emergency Medicine, North Shore University Hospital, Manhasset, NY.

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PEDIATRIC Influenza Update

S04110

A supplement to *Pediatric Emergency Medicine Reports, Emergency Medicine Reports, Primary Care Reports, Internal Medicine Alert, and Infectious Disease Alert*

February 2004

Influenza Update: Focus on Children

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From October 2003 to Jan. 9, 2004, the Centers for Disease Control and Prevention (CDC) received reports of 93 influenza-associated deaths among children younger than 18 years. The demands the annual flu season places on emergency department (ED) and urgent care facilities and the voracity of the current year's epidemic have overwhelmed many physicians. High-risk adults long have been the focus of public health programs and early diagnostic and therapeutic interventions. Influenza is responsible for significant morbidity and mortality in infants and young children, with influenza-associated hospitalization rates similar to those in adults with chronic medical conditions.[1,2]

During influenza epidemics, a diagnostic test that provides an accurate diagnosis in infants younger than 6 months of age with fever enables the clinician to provide the family with specific expectations for the disease process and minimizes unnecessary use of antibiotics.

This article reviews the current status of diagnostic testing, vaccine indications, and antiviral therapies for pediatric patients with influenza infections.

— The Editor

Epidemiology

Children account for nearly two-thirds of diagnosed cases of influenza during a typical season, with more than 30% of children living in affected communities.[3] Adults contract the illness from children, and infection rates dramatically increase in households with school-age children.

Two population-based studies highlight the direct effect of influenza on children. Evaluation of hospitalization rates in Group Health Seattle and Kaiser Northern California indicated dramatically increased rates of hospitalization in healthy children younger than 2 years of age.[1] Analysis of Tennessee Medicaid patients indicated hospitalization rates of children younger than age 2 that were similar to high-risk adults with substantive excess use of antibiotics.[2]

Influenza strikes hard in Japan. The population is long-lived, and many elderly live in homes with schoolchildren present. From 1962 to 1987, most Japanese schoolchildren were vaccinated against influenza. The vulnerable elderly were considered secondary targets for immunization. Excess influenza and pneumonia deaths dropped 40%, with 37,000-49,000 excess deaths per year averted. The laws mandating this effort were relaxed in 1987 and repealed in 1994. Subsequent vaccination rates dropped to low levels, leading to a sharply rising number of deaths.[4]

Similar findings are emerging from a study of immunizing schoolchildren with attenuated live intranasal influenza vaccine in a Texas community. Immunization rates of 50% have demonstrated the ability to prevent community epidemics and dramatically reduce excess mortality in the elderly. Immuniza-

Pediatric Influenza Ulpdate™ (ISSN 1082-3344) is published by Thomson American Health Consultants, 3525 Piedmont Road, N.E., Six Piedmont Center, Suite 400, Atlanta, GA 30305. Telephone: (800) 688-2421 or (404) 262-7436.

Vice President/Group Publisher: Brenda Mooney
Editorial Group Head: Valerie Loner
Managing Editor: Allison Mechem
Marketing Manager: Schandale Kornegay

Periodicals Postage Paid at Atlanta, GA 30304.

POSTMASTER: Send address changes to ***Pediatric Emergency Medicine Reports***, P.O. Box 740059, Atlanta, GA 30374.

Accreditation

Pediatric Influenza Update's continuing education materials are sponsored and supervised by Thomson American Health Consultants. Thomson American Health Consultants (AHC) designates this educational activity for a maximum of 1.5 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

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Intended Audience

This program is intended for pediatricians, emergency medicine practitioners, internists, and family practitioners.

Effective Dates

This activity is approved for release Feb. 1, 2004 until Jan. 31, 2005.

Questions & Comments

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Subscription Prices

1 issue *with* 1.5 AMA Category 1 credits: $25

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Objectives

After completing this activity physicians should be able to:

1) recognize the historical and clinical symptoms associated with influenza infection;
2) integrate appropriate laboratory diagnostic testing for suspected influenza into clinical practice; and
3) understand and implement into practice utilization of antiviral therapies.

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tion of schoolchildren was shown to be cost-effective when considering indirect costs of illness.[5] In another, less recent study by Monto and colleagues in Tecumseh, MI, school-age immunization reached 85%, and the incidence of influenza-like illness was one-third that of neighboring communities.[6]

Prior to the 2003-2004 influenza season, laboratory-confirmed influenza illnesses and deaths were not nationally reportable conditions. Due to an increased concern about the morbidity (especially encephalitis cases) and mortality associated with influenza in pediatrics, the CDC requested that all influenza-associated deaths be reported to state and local health departments in the 2003-2004 season. Since October 2003, a total of 93 influenza-associated deaths in children have been reported. The median age of the 93 children was 4 years, with 26% between 6 months and 23 months of age and 59% of the children younger than 5 years of age.[7] Although 38% of the children were reported to have a chronic underlying medical condition, 44% had no report of any pre-existing conditions. Another series reported that an underlying medical condition (asthma, neurologic deficits, or malignancy) was documented in 25% of children hospitalized with influenza A or B.[8]

Clinical Picture and Diagnosis

The clinical picture of influenza in young children often is subtle, with signs and symptoms mimicking other common childhood diseases. A series evaluating the prevalence of influenza in children 0-11 months of age, during the peak of an influenza epidemic, found that every third patient seen in a pediatric ED had virologically confirmed influenza infection.[9] The younger the child, the more difficult it is to distinguish influenza from other febrile illnesses.[8] In one series, the most common symptoms of influenza included fever, cough, and rhinorrhea, all nonspecific symptoms.

A retrospective 20-year review of pediatric patients with nasopharyngeal aspirates that were positive for influenza A or B, conducted in Finland, characterized the diversity of presentations. The majority of children had high fevers, and febrile seizures occurred in 12% of the children with influenza A and 9% with influenza B. Rhinorrhea and cough were present in 60% of the children and gastrointestinal symptoms (vomiting and diarrhea) were documented in 24% of the children. The classic adult symptoms of influenza (myalgias, headache, and malaise) are challenging to elicit from children younger than 3 years, secondary to normal developmental limitations. In assessments of children older than 3 years of age, 25% conveyed the presence of a headache and only 6% reported myalgias.[8]

Further confounding the ability of the clinician to make an accurate diagnosis is the diversity of clinical syndromes that may be caused by influenza. Croup, bronchiolitis, a febrile disease mimicking bacterial sepsis, and encephalitis all have been reported in association with influenza. Differentiation from parainfluenza or respiratory syncytial virus (RSV) infec-

Table 1. Commercially Available Rapid Influenza Diagnostic Tests

TEST NAME	INFLUENZA DETECTED	TIME FOR RESULTS	SENSITIVITY	SPECIFICITY	CLIA CATEGORY LAB SETTING
Now Flu A Now Flu B	A, B (distinguishes A and B)	15 min	N/A	N/A	Mod complex Hospital or referral lab
FLU OIA	A, B (does not distinguish A and B)	15 min	71.8% (range 36.7-93%)	82% (range 65.2-95.7%)	Mod complex Hospital or referral lab
QuickVue Influenza	A, B (does not distinguish A and B)	10 min	79.2% (range 74-95%)	91.9% (range 76-98%)	CLIA waived
ZstatFlu	A, B (does not distinguish A and B)	30 min	68.8% (range 48.1-96%)	83% (range 62.7-92.4%)	CLIA waived
Directigen Flu A	A	15 min	87.2% (range 39-100%)	98.1% (range 84-100%)	Mod complex Hospital or referral lab
Directigen Flu A + B	A, B (distinguishes A and B)	15 min	89.8% (A) 87.5% (B)	98.7% (A) 96.8% (B)	Mod complex Hospital or referral lab

Adapted from Uyeki TM. Influenza diagnosis and treatment in children: A review of studies on clinically useful tests and antiviral treatment for influenza. *Pediatr Infect. Dis* 2003;22:164-177.

tions requires culture or immunoassay. In addition, the young infant may require significant laboratory testing and procedures to assure a nonbacterial focus of infection.[8,10-12]

In the past, the lack of effective treatment coupled with delayed laboratory confirmation limited the ability of practitioners to develop a timely, specific diagnosis. The viral diagnosis paradigm was simply an exclusion of treatable bacterial illness in the differential diagnosis. The emergence of effective diagnostic techniques and antiviral therapy mandates a reconsideration of the evaluation of children with potential influenza-associated illnesses.

Complications

Influenza may be severe and may even lead to death, especially in children with underlying medical conditions. Secondary infections, including pneumonia and otitis media, may complicate influenza. One series reported 24% of the children developed otitis media, and pneumonia occurred in approximately 9% of the patients.[8] Pneumonia was reported in 25 of the 93 fatal cases reported for the 2003-2004 influenza season, and 15 of the children had an invasive bacterial co-infection.[7] Severe presentations and complications also have been associated with influenza and include encephalitis, Guillain-Barré type polyradiculopathy, and myositis.[8]

Diagnostic Testing

Exclusively pediatric studies comparing the accuracy of a clinical diagnosis to laboratory-confirmed influenza virus infections have not been conducted. Studies consisting primarily of adult patients have shown the highest predictive value of any case definition for influenza was 40% when compared with viral culture.[13] Immunofluorescence staining may be performed on respiratory specimens (nasopharyngeal swabs, aspirate, or nasal swab with adequate epithelial cells) for the detection of influenza viruses.

Direct immunofluorescence antibody (DFA) tests and indirect immunofluorescence antibody (IFA) tests may be performed on respiratory samples to detect influenza viruses. These tests usually can be performed at a hospital or reference lab within 2-4 hours, but the specimen quality (adequate number of epithelial cells in the specimen) and technician experience are important. Three studies of the use of DFA for influenza A (compared to viral culture), revealed a median sensitivity of 62% (range 45-65%) and the median specificity was 98% (range 92-99.7%).[14-17] Three studies that compared IFA for influenza A and B to viral culture revealed a median sensitivity of 73.9% (range 59.8-90%) and a median specificity of 97% (range 93-97%).[17-19] Both IFA and DFA only are available to hospital-based physicians, have a high rate of false negative results, and require a minimum of 2-4 hours for test results.

The availability of CLIA (Clinical Laboratories Improvement Act) made rapid diagnostic kits for influenza available for diagnosis and timely intervention. Rapid influenza testing is reasonably accurate for detecting influenza infections in pediatric patients. *(See Table 1.)* False negative results may occur, but false positives are infrequent. Therefore, if the diagnosis of influenza is suspected in a moderately to severely ill child, more definitive testing may be indicated.

The development of a selective strategy for the use of the rapid influenza test is pragmatic. Each patient is not necessarily tested; rather, the test is used to calibrate the clinician's clinical acumen and to provide confirmation of local disease presence.

Table 2. Antiviral Drugs for Treatment of Influenza

DRUG MECHANISM	INDICATION	ACCEPTABLE AGE GROUPS	DOSAGE FOR ACUTE TREATMENT	POTENTIAL ADVERSE EFFECTS
Amantadine M2 inhibitor	Influenza A	Treatment > 1 year of age Prophylaxis > 1 year of age	1-9 years of age: 5 mg/kg/day divided BID (maximum dose 150 mg)	CNS side effects Rapid resistance
Rimantadine M2 inhibitor	Influenza A	Treatment > 14 years of age Prophylaxis > 1 year of age	> 14 years of age: 100 mg BID	Rapid resistance
Zanamivir neuraminidase inhibitor	Influenza A and B	Treatment > 7 years of age (orally inhaled powder)	> 7 years 10 mg BID for 5 days	Caution with history of bronchospasm. Not approved for prophylaxis.
Oseltamivir neuraminidase inhibitor	Influenza A and B	Treatment > 1 year of age Prophylaxis > 13 years of age	< 15 kg: 30 mg BID for 5 days > 15 kg and < 23 kg: 45 mg BID for 5 days > 23 kg and < 40 kg: 60 mg BID for 5 days > 40 kg: 75 mg BID for 5 days	Mild GI side effects
Ribavirin Unknown	In vitro activity against RSV, influenza, and other viruses	Not approved	No approved dosage	Not approved for treatment of influenza infections.

Key: RSV—respiratory syncytial virus; CNS—central nervous system; GI—gastrointestinal

In certain situations, use of the rapid test may confirm a specific viral diagnosis; avert unnecessary diagnostic testing; provide for early, effective antiviral treatment; and reassure concerned parents about the lack of indication for antibiotics.

The use of diagnostic tests has led to a significant decrease in the unnecessary use of antibiotics, and logically should lead to a reduction in the emergence of antibiotic resistance.[20,21] The use of laboratory and radiographic testing also has been shown to be significantly reduced through the use of the rapid influenza tests, leading to decreased patient charges.[10,21] Especially in infants and younger children, a positive influenza test has been shown to decrease the number of complete blood counts, blood cultures, urine cultures, cerebral spinal fluid studies, and chest radiographs.[10] In addition, the use of rapid diagnostic testing has been shown to decrease the length of stay in the ED for patients with a positive rapid test for influenza.[10]

Treatment

Currently, three antiviral drugs—amantadine, oseltamivir, and zanamivir—are approved for the treatment of influenza in children, and two other drugs—rimantadine and ribavirin—have been used. *(See Table 2.)*

Amantadine. About 30 years ago, specific antiviral therapy of influenza began with the introduction of amantadine, a drug that targets the M2 membrane protein of influenza A. The drug has not been studied in an exclusively pediatric population, but two studies have shown a reduction in the mean duration of fever.[22,23] It also has been shown to decrease the frequency of headaches and gastrointestinal symptoms (nausea and vomiting)[22,23] and to reduce the duration of uncomplicated influenza A and B illness by one day when compared to placebo. Amantadine has not been demonstrated to be effective for the prevention of serious influenza-related complications, and the majority of the studies have been conducted in patients with uncomplicated illnesses. Although the development of amantadine resistance has not been adequately assessed, a trend toward a rapid emergence of resistance and lack of activity against influenza type B reduces its usefulness.

It also is effective as a prophylactic agent during epidemics in both adults and children older than 1 year.[24] Neurologic and gastrointestinal side effects may be significant in very young and elderly patients. Resistance has been documented within single households, with treated index cases transmitting resistant virus to other family members.[25]

Rimantadine. Although rimantadine currently only is approved for chemoprophylaxis of influenza type A infections among children, some experts consider it acceptable treatment for the illness. Rimantadine, similar to amantadine, has been

shown to decrease the duration of uncomplicated influenza A illness when administered within 48 hours of the onset of illness.[26] Resistance has been shown to develop rapidly with the use of rimantadine, and one study demonstrated a prolonged viral excretion in children treated with rimantadine.[26] Rimantadine has been shown to have a decreased incidence of central nervous system (CNS) side effects when compared to amantadine.

Zanamivir. Zanamivir is a neuraminidase inhibitor and has activity against both influenza A and B. Clinical studies in experimental and natural infection demonstrated decreased length of viral shedding, symptoms, and severity in both type A and B influenza illnesses.[27,28] Ongoing studies of the neuraminidase inhibitors have shown efficacy in childhood. A double-blind, placebo-controlled study of zanamivir in the 1998-1999 northern hemisphere flu season recruited 471 children with flu-like symptoms. Three hundred forty-six had culture-proven influenza, and inhaled diskhaler therapy significantly shortened time to alleviation of symptoms and time to resumption of normal activity. The treatment group also used less relief medications and there was a reduction in associated complications (16%) and antibiotic use (12%).[29]

Questions were raised regarding respiratory function deterioration in patients with existing chronic obstructive pulmonary disease (COPD) and asthma. Bronchospasm has occurred in patients with asthma.[28,30] The package insert contains important precautionary information regarding the use of zanamivir with underlying airway disease. The drug is taken as a five-day course using a proven diskhaler design. It is indicated for patients ages 7 and older who have signs and symptoms of influenza A and B of fewer than 48 hours duration.

Oseltamivir. The desire for an orally active drug led to the development of oseltamivir (Tamiflu). Oseltamivir is a neuraminidase inhibitor that has activity against both influenza A and B. Oseltamivir has been approved for treating uncomplicated influenza infections in children older than 1 year and also has been approved for use as a chemoprophylaxis agent in children older than 13 years.

A study of 695 patients ages 1-12 years showed a 36-hour, or 26%, reduction in duration of influenza. The incidence of otitis media was reduced by 44%.[31] Specific efficacy was demonstrated with influenza B infection in other studies, with a decrease of symptom duration by 25%.[30,32] Oseltamivir was well-tolerated in clinical trials, with no safety issues raised. In adult, adolescent, and child studies, nausea was reported, with a greater incidence of emesis over placebo of 5.8%. The recipients described the gastrointestinal symptoms as transient and mild.[33,34] Discontinuation of medication due to adverse events was 1.8% in the oseltamivir group vs. 1.1% with placebo.[31] Prior studies with adolescents and adults indicate significant reduction of gastrointestinal symptoms with concomitant consumption of food.[33] Resistant strains were uncommon and represented viruses with limited infectivity in humans.

Ribaviron. Minimal information is available regarding the use of ribaviron for the treatment of influenza in children. Two randomized controlled studies compared ribaviron to the use of placebo in children with influenza. Aerosolized ribaviron, given to hospitalized children who had fewer than 48 hours of symptoms reduced the mean duration of fever.[35] Oral ribaviron was evaluated in a single double-blinded controlled study in girls 8-16 years of age and found significantly reduced symptoms 24 hours after starting the medication and decreased viral shedding. Neither study reported any significant adverse effects.[36]

Prophylaxis. Chemoprophylactic drugs are an adjunct to vaccination in the prevention and control of influenza. The neuroaminidase inhibitors have been shown effective for prevention of influenza infection. Zanamivir once a day was 79% effective for the prevention of influenza transmission within families with a confirmed index case.[37] Orally administered oseltamivir 75 mg once a day protected close family contacts against influenza by 92% and interrupted transmission within households by 89%.[38,39] Post-exposure, the placebo group had a 12% incidence of influenza, compared with a 1% incidence in the prophylaxis group. The U.S. Food and Drug Administration (FDA) has indicated oseltamivir for prophylaxis in adolescents and adults ages 13 and older.

It has been suggested that use of family prophylaxis after treatment of the index case may be the most effective use of the medication. It not only protects familial contacts but also can serve to reduce community exposure. Family physicians are in a unique position to treat the whole family when an index case is identified. Pediatricians will need to form effective alliances with internists and family physicians to effectively reach the parents of children with influenza.

Reducing Complications and Antibiotic Use

The serious complications of influenza include bacterial pneumonias, Reye syndrome, and prolonged recovery of high-risk patients. The increased frequency of otitis media and other respiratory infections in children with influenza is under-appreciated. With proper antiviral treatment of influenza, a substantive reduction of antibiotic usage has been demonstrated. This reflects a real decrease in otitis media occurrence, as well as the desired reduction in the overuse of antibiotics for primary viral infection.

In the oseltamivir trials in children ages 1-12 years, 21% of placebo recipients and only 12% of treated subjects had documented otitis media.[30] The 44% reduction in clinical diagnosis was paralleled by a 40% reduction in antibiotic usage.[31] The zanamivir trials of children ages 5-12 years showed a 30% reduction in bacterial complications, with a 20% reduction in antibiotic use.[29] Effective treatment of primary viral infections can reduce otitis morbidity and antibiotic usage.

In pivotal clinical trials, the neuraminidase inhibitors showed efficacy with one- to two-day decreases in time to alleviation of all significant symptoms of influenza. Early FDA examination

and subsequent professional commentary questioned this apparent marginal benefit from therapy. Health maintenance organizations and other third-party payers also questioned utility, and frequently excluded the medications from their panels. This marginality of efficacy contrasted strongly with clinical observations of patients, physicians, and investigators using the medications. In an effort to reconcile clinical impressions in practice with clinical trial data, investigators followed 1408 patients using prescribed zanamivir in Australia during the 1999 flu season.

Symptom relief was reported by more than 50% of patients within 24 hours and by 77% within 48 hours.[40] Of the 400 elderly patients, 78% were satisfied with their treatment, with 59% experiencing symptom relief within 24 hours.[41] The survey concluded that zanamivir was associated with an early return to normal activities. The investigators also noted that patients with influenza had a protracted cough. Even in treated influenza patients, the cough persisted after systemic symptoms of fever, headache, myalgia, and malaise had resolved. They speculated that residual cough prolonged the end point in the clinical studies and, thus, caused an underestimation of the clinical effect of treatment.

The identification and treatment of primary viral infections remains a significant challenge to pediatric medicine. It also represents a significant opportunity to reduce an ongoing burden of illness. The technology for effectively preventing, diagnosing, and treating influenza has been demonstrated. Outpatient clinics, emergency rooms, and urgent care centers, as well as private physician offices, need to organize specifically to meet the challenge of early intervention in influenza epidemics. Telephone triage systems need to efficiently screen those with classic symptoms of influenza and promptly direct them to where they can be evaluated and treated with minimal delay. Specific time slots dedicated to prompt evaluation and treatment of infectious disease must be set aside during anticipated flu seasons.

The widespread implementation of influenza prevention and treatment in pediatric populations would provide benefit not only to the index cases but also to household contacts and vulnerable fragile elderly in the community. The antiviral treatment and chemoprophylaxis of contacts of influenza victims will serve as a model for treatment of other specific viral illness as newer antiviral agents that are readily visible in the drug pipeline become available to the practitioner.

Immunization. The U.S. Advisory Committee on Immunization Practices (ACIP) has issued its recommendations for the 2004-2005 influenza season. ACIP has recommended that all children 6-23 months of age be vaccinated annually against influenza beginning in the fall of 2004. Children younger than 9 years of age who previously have been unvaccinated should receive two doses one month apart. ACIP continues to strongly recommend vaccination of children with chronic medical problems. The recommendation to vaccinate healthy children in the 6-23 month age group is based on studies that showed that previously healthy young children account for the majority of hospitalizations for pediatric influenza.[42] Cost calculations have suggested that, for healthy children, vaccination against influenza would be cost-effective[5] and would decrease influenza-associated morbidity and mortality in the adult population because of the important role of children in the dissemination of influenza.[4] Vaccination programs should start in October and target adults older than 50 years, children 6-23 months of age, high-risk patients of any age and their household contacts, and health care workers. The attenuated live intranasal vaccine (FluMist) is an expensive option ($55.20/dose) for healthy individuals 5-49 years of age who do not have contact with immunocompromised patients. Children 6-35 months may receive 0.25mL/dose of Fluzone, and patients older than 35 months may receive 0.50 mL/dose of Fluvirin or Fluzone.

Future Directions and Considerations

The use of real-time influenza reporting systems enables clinicians to either include or exclude the possibility of influenza through community epidemiology. The use of quick diagnostic kits makes a positive diagnosis of the viral infection possible, and increased usage may prevent many needless exposures to unnecessary antibiotics.

With proper local epidemiologic surveillance and available laboratory tests, more precise diagnosis will be facilitated, and enhanced use of antiviral agents promoted. More than ever, precision in defining the etiologic agents is not only desirable, but also necessary.

(The authors wish to acknowledge the contributions of Katalin Koranyi, MD, Professor of Clinical Pediatrics, Section of Infectious Disease, Department of Pediatrics, College of Medicine, The Ohio State University, Columbus.)

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CME Objectives

The CME objectives for *Pediatric Influenza Update* are to help physicians:

1) recognize the historical and clinical symptoms associated with influenza infection;
2) integrate appropriate laboratory diagnostic testing for suspected influenza into clinical practice; and
3) understand and implement into practice utilization of antiviral therapies.

evaluation of 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (ribavirin) in a double-blind study during an outbreak of influenza. *Ann NY Acad Sci* 1977;284:272-277.
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Physician CME Questions

1. Gastrointestinal symptoms of vomiting and diarrhea occur in how many children with influenza?
   A. Approximately 24%
   B. More than 50%
   C. More than 75%
   D. Almost all

2. The findings of a Texas study with a 50% immunization rate for schoolchildren demonstrated:
   A. immunization of schoolchildren was shown to be cost effective when considering indirect costs of illness.
   B. immunization made no difference.
   C. immunization prevented community epidemics.
   D. immunization dramatically reduced excess mortality in the elderly.
   E. A, C, and D only are correct.

3. Which of the following statements about the presentation of influenza in children is correct?
   A. The infection only presents as classic bronchiolitis.
   B. Differentiation from parainfluenza or respiratory syncytial virus (RSV) infections may be accomplished without culture or immunoassay.
   C. Febrile seizures may occur in association with an influenza illness.

4. Severe presentations and complications associated with influenza include encephalitis, Guillain-Barré type polyradiculopathy, and myositis.
   A. True
   B. False

5. Which of the following may be a complication of influenza?
   A. Bacterial co-infection
   B. Otitis media
   C. Pneumonia
   D. All of the above

6. Effective treatment of primary viral infections can reduce otitis media occurrence and antibiotic usage.
   A. True
   B. False

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge.

To clarify confusion surrounding any questions answered incorrectly, please consult the source material. After completing this activity, you must complete the enclosed evaluation form and return it in the reply envelope provided to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you.

Answer Key

1. A
2. E
3. C
4. A
5. D
6. A