Apnea of Prematurity and Sudden Infant Death Syndrome

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Contents

Abstract

Apnea of prematurity is a self-resolving, yet very common condition in preterm infants. Recent observational data suggest that the intermittent hypoxemia often occurring with it may be associated with an increased risk of adverse outcome, including cerebral palsy, retinopathy of prematurity, and death. Treatment should follow an incremental approach, starting with head elevated positioning, followed by caffeine administration and nasal respiratory support.

Sudden infant death syndrome has decreased markedly in incidence following primary prevention campaigns in many countries, yet continues to be a leading cause of death beyond the neonatal period. Although still incompletely understood, it seems that death is the result of an external trigger (e.g., prone sleep position) occurring in a vulnerable infant (e.g., born to a mother who smoked during pregnancy) during a critical developmental period (e.g., 2–4 months of age). Memory monitor recordings obtained during SIDS suggest that bradycardia, probably resulting from severe hypoxemia, is the primary abnormality in the sequence of events ultimately resulting in these deaths. Prevention should focus on a safe sleep environment, i.e., supine sleep position, a smoke-free environment, avoidance of overheating, use of a sleeping bag, and room but not bed sharing.

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List of Abbreviations

AAP	American Academy of Pediatrics
ALTE	Apparent life-threatening event
AOP	Apnea of prematurity
BPD	Bronchopulmonary dysplasia
CDC	Centers for Disease Control
CI	Confidence interval
CO_2	Carbon dioxide
IH	Intermittent hypoxemia
LQTS	Long-QT-syndrome
MCAD	Medium-chain acyl-CoA dehydrogenase
N-CPAP	Nasal continuous positive airway pressure
N-IPPV	Nasal intermittent positive pressure ventilation
NNT	Number needed to treat
OR	Odds ratio
PaO_2	Partial pressure of oxygen in arterial blood
PAR	Population-attributable risk
RCT	Randomized controlled trial
ROP	Retinopathy of prematurity
RR	Relative risk
SIDS	Sudden infant death syndrome
SpO_2	Arterial oxygen saturation measured by pulse oximetry
TPN	Total parenteral nutrition
VLBW	Very low birth weight

66.1 Salient Points

- Apnea of prematurity is a self-resolving and very common condition in preterm infants.
- The intermittent hypoxemia accompanying it may be associated with an increased risk of adverse outcome (cerebral palsy, retinopathy of prematurity, and death).
- Treatment consists of head elevated positioning, followed by caffeine administration and nasal up to nasal respiratory support.
- The incidence of sudden infant death syndrome (SIDS) has markedly decreased even if it remains a leading cause of death in the postneonatal period.
- It seems that death is the result of an external trigger (position) occurring in a vulnerable infant during a critical developmental period.
- Prevention should focus on a safe sleep environment (supine positioning), a smoke-free environment, and avoidance of overheating.

66.2 Apnea of Prematurity (AOP)

66.2.1 Introduction

Apnea of prematurity (AOP) is a developmental and thus self-resolving disorder, which nonetheless may cause serious long-term sequelae through accompanying hypoxemia. Almost every infant born at less than 29 weeks gestation exhibits AOP, but little was known when it became potentially harmful. Recently, a secondary analysis of pulse oximeter saturation (SpO_2) and pulse rate data recorded for a mean duration of 68 days in 1035 participants in the Canadian Oxygen Trial (COT), who were born at 23–27 weeks GA and survived to 36 weeks postmenstrual age (PMA), showed the following (Poets et al. 2015):

- Mean percentages of recorded time with hypoxemia (pulse oximeter saturation (SpO_2) <80% for at least 10 s) for the least and most affected 10% of infants was at 0.4 and 13.5%, respectively, while bradycardia (pulse rate <80/min.) was rarer at 0.1 and 0.3%.
- Being in the highest decile for % time with intermittent hypoxemia (IH) was associated with three to fivefold increased odds of developing the primary outcome of death beyond 36 weeks or disability at 18 months, with these associations being significant only for events lasting at least 1 min.
- Odds ratios for secondary outcomes (motor impairment, cognitive, or language delay and severe retinopathy of prematurity) were similarly increased after prolonged hypoxemia.
- Bradycardia, in the absence of concomitant hypoxemia, did not significantly add to the risk of adverse outcome.
- The severity of IH, expressed as the area-under-the-curve (AUC), and the rate with

which desaturation occurred, added little prognostic value.
- Associations between hypoxemic exposure and adverse outcomes were stronger at later postnatal ages (i.e., at 8–10 week) and for infants assigned to a target range of 91–95% compared to a target range of 85–89% SpO_2.

Thus, of the three components contributing to AOP (apnea, bradycardia, hypoxemia), it seems prudent to focus on the avoidance of IH, particularly episodes lasting for 1 min, or longer, if we want to avoid adverse effects of AOP in extremely preterm infants. Up to now, however, most studies on interventions for AOP focussed on apnea.

Although not fully in line with the above data, the approach taken in the author's institution for the last 10 years has been to grade the intensity of the treatment provided for AOP based on a severity score that relies largely on the nurses' acute intervention to events (e.g. stimulation, bagging; Fig. 1). Neither the score nor any treatment threshold used with it has ever been validated. However, the low rates of retinopathy of prematurity (ROP; <2% for stage 3 or higher in infants <1500 g birth weight in 2010–2015) and high Bayley scores (Moll et al. 2011) associated with implementation of this apnea scoring paradigm suggest its potential as a protocol that warrants further study. In any case, such a severity score may only serve as an example for how apnea severity may be assessed more objectively without documentation via continuous recordings, which would be preferable but is yet impractical in most units.

66.2.2 Treatment

In the following, interventions to improve AOP will be grouped into those that have been shown to be beneficial and those where the effect is questionable and/or needs further study (Table 1).

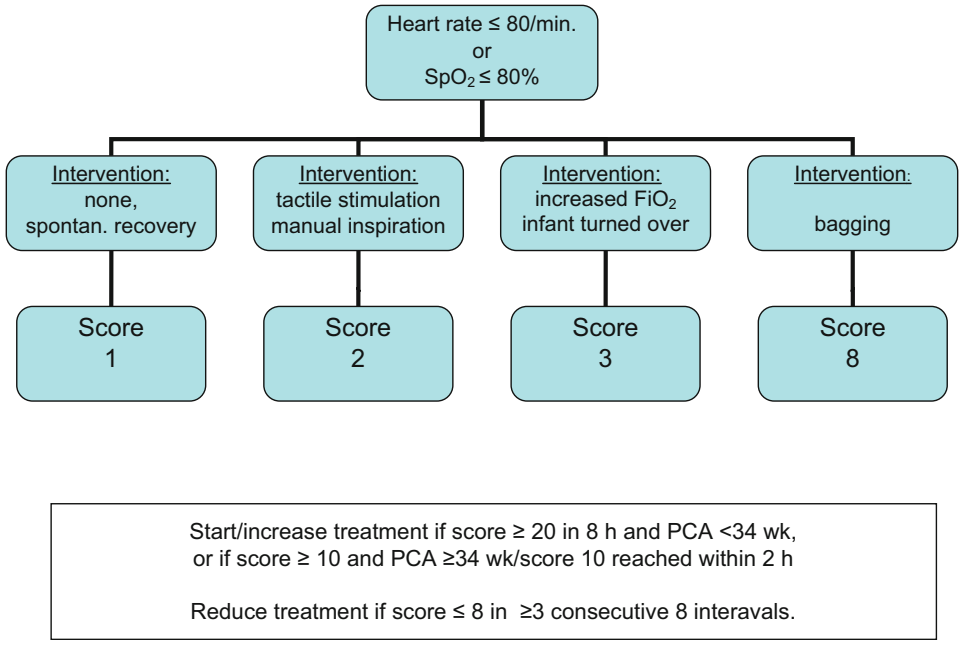

Fig. 1 A proposed apnea severity score to standardize assessment across different raters/infants. The values in the lower row of boxes indicate the respective score. The threshold for an increase in treatment severity is lower in more mature infants as these are considered more vulnerable to the detrimental effects of intermittent hypoxemia (Modified based on Poets CF (2010). Interventions for apnoea of prematurity: a personal view. Acta Paediatr 99; 2172–2177, with permission)

Table 1 Suggested incremental treatment plan for AOP

First Step: 15° head-up tilt position
Second Step: Caffeine[a]
Third Step: Variable flow CPAP or synchronized N-IPPV
Fourth Step: Intubation and mechanical ventilation[b]

[a]Consider caffeine as first-line treatment in infants <29 weeks GA

[b]High-dose caffeine or doxapram may be considered as alternatives in infants who continue to exhibit recurrent hypoxemia despite mechanical ventilation

66.2.2.1 Interventions with Proven Benefit

Head-Elevated Positioning

While a recent Cochrane analysis demonstrated *no* advantage of the prone position in reducing apnea rates in preterm infants (data on intermittent hypoxia were not reported), a head-elevated 15° tilt position was associated with a 49% reduction in desaturations to <85% in a study involving 12 preterm infants. A reinvestigation of the effectiveness of this position, however, triggered by the observation that infants appear more comfortable when only the chest and head rather than the entire body are being tilted showed only a modest (−6%) and nonsignificant reduction in hypoxemia rates in the head elevated tilt compared to the horizontal position (Reher et al. 2008), and also no significant advantage (−22%) for the head-and-chest elevated position. This much less clear advantage of the head-up tilt position may be due to the fact that several infants in the earlier study had received no other treatment for AOP, whereas in the more recent one, all had received methylxanthines and/or continuous positive airway pressure (CPAP) in addition to positioning (Reher et al. 2008). Thus, a head-up tilt position may be considered a first step in an incremental treatment plan for AOP, while this intervention may be less effective in infants already receiving other treatments for AOP, such as caffeine or CPAP (see below).

Continuous Positive Airway Pressure (CPAP) and Synchronized Nasal Ventilation (S-NIPPV)

CPAP has been shown to reduce extubation failure in preterm infants and can be applied via a nasopharyngeal tube or (bi-)nasal prongs. Reintubation rates are 40% lower with the latter (relative risk (RR) 0.59 [95%-confidence interval (CI) 0.41; 0.85], number needed to treat (NNT) 5) (De Paoli et al. 2008), suggesting nasal prongs as the preferred patient interface when applying CPAP. An extension of CPAP is nasal intermittent positive pressure ventilation (N-IPPV), with better effectiveness than CPAP in preventing extubation failure if used in synchrony with the infant's own breathing efforts. Typically, an inspiratory pressure of 15–20 cm H_2O, applied at a rate of 10–20/min, is combined with a CPAP level of 5–6 cm H_2O. A recent meta-analysis investigating the effects of synchronised and nonsynchronized nasal ventilation versus CPAP on respiratory failure rates found a significant effect only for the former, making this the preferred mode of nasal ventilatory support if a trial of CPAP fails (Lemyre et al. 2014). Interestingly, gastric distension, a theoretical concern with nasal ventilation, was not an issue in the studies contributing to this meta-analysis (Lemyre et al. 2014).

An even more recent study investigated different synchronized nasal ventilation system in 19 infants at a mean PMA of 30 week and reported a decrease in bradycardia (<80/min) and desaturation (<80%) from 6.1/h with CPAP to 2.9/h with S-NIPPV. With nonsynchronized NIPPV, this rate was similar to that with CPAP (5.9 events/h) (Gizzi et al. 2014). An earlier study comparing nonsynchronized N-IPPV with nasal CPAP, delivered via a variable flow CPAP device that reduces work of breathing (InfantFlow, CareFusion, San Diego, CA), showed a decrease in bradycardia and desaturation rate by approximately 50% compared to both, nonsynchronized N-IPPV or CPAP (Pantalitschka et al. 2009). Thus, a reduced work of breathing and/or effective synchronization with the infant's own breathing efforts may be key to success for nasal respiratory support applied to ameliorate AOP.

Caffeine

Methylxanthines increase chemoreceptor sensitivity as well as respiratory drive and can also improve diaphragmatic function. Of the substances available, caffeine has a wider therapeutic range and

fewer side effects than theophylline. Its effectiveness in improving patient outcome was proven in a large placebo-controlled RCT enrolling over 2000 infants (the CAP study (Schmidt et al. 2007)). Caffeine (or placebo) was started during the first 10 postnatal days in infants of 500–1250 g birth weight at a dose of 5−10 mg/kg caffeine citrate in infants considered eligible for caffeine treatment and given until no longer considered necessary for AOP treatment. Mechanical ventilation, CPAP, and oxygen could all be discontinued approximately 1 week earlier in infants treated with caffeine. Somewhat unexpected, and not a primary outcome, was the finding of a 40% lower risk of bronchopulmonary dysplasia (BPD; 36% vs. 47%; OR 0.6; 95% CI 0.5; 0.8), a 30% lower risk of developing a symptomatic patent ductus arteriosus (OR 0.7; [0.5; 0.8]), and a 40% reduction in the risk of developing stage 4 or 5 retinopathy of prematurity (ROP) or requiring treatment for ROP in the caffeine group (OR 0.61 [0.42; 0.89]) (Schmidt et al. 2007). Most important, however, are the data on the primary outcome, showing a 23% reduction in death or disability at 18 months corrected age in addition to a reduction in cerebral palsy in infants in the caffeine group (Schmidt et al. 2007).

Results from the 5-year follow-up of this study still showed an effect of caffeine on death or disability, but this was no longer significant. Neonatal caffeine therapy, however, reduced motor impairment (OR 0.66; 0.48; 0.91) (Schmidt et al. 2012). Motor dysfunction not associated with cerebral palsy or cognitive impairments is referred to as developmental coordination disorder. At 5 years of age, this condition was found in 11% of caffeine-group infants compared to 15% of placebo-group infants. Regarding other long-term (side)effects, sleep studies, performed in 201 former CAP participants at age 5–12 years, showed no difference in sleep disorders in subjects treated with neonatal caffeine compared to placebo (Marcus et al. 2014).

In subgroup analysis, the effect of caffeine on the primary outcome was found to be restricted to those requiring ventilatory support at randomization, i.e. caffeine had no effect on death or disability in infants *not* requiring CPAP or IPPV. Interestingly, the reduced duration of the need for ventilatory support was only evident in those who were randomized within the first 3 postnatal days, and the effect on death or disability was only significant for infants receiving at least 3.5 mg/kg/day of caffeine base (7 mg/kg/day caffeine citrate). Also in secondary data analysis, a significant difference in the rate of cerebral palsy between caffeine- and placebo-group infants was only found in those receiving caffeine for at least 45 days. Thus, caffeine administration should be started within the first 3 days of age in infants <1250 g requiring respiratory support and being likely to develop AOP.

It is important also to consider when to discontinue caffeine treatment. In the CAP study, caffeine was given until a mean PMA of 34.4 weeks (Schmidt et al. 2007). However, caffeine continues to be effective in reducing intermittent hypoxia rates until 35 weeks PMA (Rhein et al. 2014). With no current standards for discontinuing caffeine therapy, the use of an apnea severity score such as that proposed in Fig. 1 may provide a treatment guideline in the clinical setting.

At what dose should caffeine be given? First, it has to be remembered that caffeine is usually available as caffeine citrate, in which the active component (caffeine) comprises only 50% of the total dose. In this chapter, all data will be on this active component. In the CAP study, a loading dose of 10 mg/kg (iv or orally) and a maintenance dose of 2.5–5 mg/kg once daily were used. Another recent randomized controlled trial compared a loading dose of 40 mg/kg caffeine (maintenance dose 10 mg/kg/day) with a “conventional” 10/2.5 mg/kg regimen in 234 infants born at a mean GA of 27 weeks. Infants in the high dose group had only half the risk of failing extubation within 48 h of caffeine loading or to require reintubation and mechanical ventilation or doxapram within 7 days of caffeine loading (15.0% vs. 29.8%, RR 0.51 [0.31; 0.85]) (Steer et al. 2004). They received mechanical ventilation for 14.4 days (SD 11.1), compared to 22.1 (17.1) days for infants in the lower dose group. This better efficacy was not at the expense of an increased risk of side effects, including no difference in Griffith’s mental development scales at age 12 months. Given the

extremely sparse data on doxapram (see below), clinicians may consider starting caffeine at the standard dose of 10 mg/kg loading, 5 mg/kg/day maintenance, but to switch to a higher dose if AOP persists in an occasional infant. It has to be kept in mind, however, that the follow-up study on high dose caffeine was underpowered to detect a difference in neurodevelopmental outcome between the low- and the high-dose group that at this dose the serum level should occasionally be checked to identify those approaching toxic levels (>50 mg/l), and that a recent RCT testing the same dose as used by Steer et al. (2004) was stopped prematurely because of an unexpectedly high rate of cerebellar hemorrhages (36% vs. 10%) in infants receiving high-dose caffeine (McPherson et al. 2015). There are no indications that tachyphylaxis occurs with caffeine, but higher doses and a 12-h dosing interval may be necessary in infants approaching term-equivalent age because of a more rapid caffeine metabolism in this age group.

66.2.2.2 Interventions That Are Potentially Effective but Require Further Study

Doxapram

Doxapram stimulates peripheral chemoreceptors at low and central ones at high doses. It shows a clear dose–response curve, with a 50% reduction in apnea rate occurring in 47%, 65%, 82%, and 89% of infants at doses of 0.5, 1.5, 2.0, and 2.5 mg/kg/h, respectively. In an own longitudinal study, desaturation rates to ≤80% SpO_2 were reduced from a median of 8/h to 2/h, with this effect continuing for the follow-up period of 6 days (Poets et al. 1999a). Most studies used a continuous intravenous infusion, although some suggest that the iv solution may also be given orally at twice the dose with good effect (enteral absorption is approximately 50%) (Poets et al. 1999a). Short-term side effects become quite common at doses above 1.5 mg/kg/h and include irritability, myoclonus, elevated blood pressure, and gastric residuals. Of concern is the fact that the long-term effects of doxapram are unknown. This is particularly worrisome given that in a study on factors associated with poor development in extremely low birth weight infants, the only difference found was that infants with developmental delay (defined as a Mental Development Index <70) had received a mean cumulative doxapram dose of 2233 mg, compared to 615 mg in matched controls without delay ($p < 0.01$) (Sreenan et al. 2001). Although such a retrospective analysis cannot distinguish whether this reflects sequelae of severe AOP (for which doxapram had been given) or a direct drug effect, it clearly raises concern. In the CAP study (Schmidt et al. 2007), placebo group infants not only had been more likely to develop cerebral palsy but were also three times more likely to have received doxapram. Given these data (or lack thereof), doxapram cannot be recommended as a standard treatment for AOP, although it seems to be rather widely used in some countries.

Oxygen Administration

That oxygen stabilizes neonatal respiration was first observed in 1923 and responsible for an epidemic in ROP in the following years. Several crossover trials in infants with and without BPD have since shown that the application of low-flow oxygen results in a reduced rate of apnea and IH. Application of this therapy, however, has to be weighed against side effects potentially resulting from oxygen toxicity. The issue has resurfaced with the recent data from RCTs comparing an SpO_2 target range of 85–89% with 91–95%. As perhaps to be expected, there was a higher rate of ROP in infants randomized to the higher range, but – unexpectedly – also a lower mortality in two of these studies, which was confirmed in meta-analysis (Saugstad and Aune 2014). Interestingly, however, the study achieving the widest separation in SpO_2 between study groups was also that where no difference was found for either ROP or mortality (Schmidt et al. 2013). Infants randomized to the lower target range indeed also had more episodes of IH (SpO_2 < 80%) (Poets et al. 2015). Whether these data are sufficient to recommend keeping the SpO_2 at a

target range of 91–95% to prevent some episodes of IH is yet open to debate.

Increased Inspiratory CO_2 Concentration

One determinant of respiratory drive is CO_2. If CO_2 levels fall below the eupneic baseline value, apnea occurs. A Canadian group performed an RCT in 87 infants of 27–32 weeks GA to test whether adding 0.5 l/min. of CO_2 to the inspired air (corresponding to a CO_2 concentration of 1%) was as effective as theophylline in reducing apnea duration and rate (Alvaro et al. 2012). They found that apnea time indeed decreased with CO_2 inhalation from 183 ± 44 to 101 ± 26, 105 ± 29, and 94 ± 26 s/h during the 3 days of intervention, but this was still twice as high as the apnea time seen in infants randomized to theophylline. No data on oxygenation were provided.

Red Blood Cell Transfusions

An increase in respiratory drive resulting from an increased tissue oxygenation is also one of the proposed mechanisms for red cell transfusions potentially to ameliorate AOP, and anemia has indeed been implicated in the pathophysiology of AOP. It would thus seem only logical to hypothesize that giving a blood transfusion is an effective treatment modality in infants with AOP who are anemic. Data on the effect of blood transfusions on the frequency of these episodes, however, are conflicting. In two crossover studies from the author's group, no effect of transfusion was found on bradycardia and IH. In contrast, others found an age-dependent improvement in frequency and severity of IH after transfusion beyond the first week of life when IH events begin to increase. A meta-analysis of 4 RCTs comparing the effects of a liberal with a more restrictive transfusion policy found no statistically significant differences in the combined outcomes of death or serious morbidity at first hospital discharge (Whyte and Kirpalani 2011). While this result doesn't exclude some minor effects on apnea rate, it clearly suggests that such effects, if they exist, do not improve clinical outcomes and make it therefore difficult to justify blood transfusions as a means to treat AOP.

Oscillating Waterbed/Mechanosensory Stimulation

The theory behind this intervention is that entrainment can be achieved between an infant's own breathing rhythm and an external rhythm generator, e.g., an inflatable mattress connected to a respirator. A meta-analysis of 3 RCTs testing this intervention, involving a total of 165 infants, showed no effect on apnea or bradycardia. This may be explained by the observation that synchronization with an external rhythm generator is significantly better beyond than before 35 weeks GA, but at that age AOP is no longer a major issue. As a result, this intervention has largely been abandoned. More recently, however, it has resurfaced in the form of a stochastic mechanosensory stimulation, where actuators are embedded in a specially designed mattress (Bloch-Salisbury et al. 2009) trying to simulate the cutaneous stimulation given by maternal licking of the newborn as observed in many animal species after birth. Using such a device in a crossover design in 10 preterm infants with a mean PMA of 33 weeks and a study duration of 2 × 1.5 h, a 65% reduction in time with $SpO_2 < 85\%$ was found. Confirmation of the effectiveness of this approach in a larger sample and longer study duration is necessary.

In summary, treatment for AOP may follow an incremental approach, starting with infant care procedures such as prone head-up tilt positioning, followed by methylxanthines and CPAP/N-IPPV.

66.3 Sudden Infant Death Syndrome (SIDS)

Sudden deaths in infants are known since biblical times, but it was only in 1970 that Bergman et al. coined the term SIDS. More recently, it was redefined by an expert panel as "the sudden unexpected death of an infant <1 year of age, with onset of the fatal episode apparently occurring during sleep, that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the

circumstances of death and the clinical history." To facilitate research, this definition was stratified into cases with the "classic" features of SIDS present and completely documented (so-called Category 1A SIDS), those with these features present but incompletely documented (IB), and those meeting Category I criteria except for one or more of the following: age <3 weeks or >270 days, similar deaths in siblings, close relatives or infants in the custody of the same caregiver, perinatal conditions such as a history of premature birth, suspected mechanical suffocation, or marked inflammatory changes not sufficient to be assigned a cause of death (i.e., Category II) (Krous et al. 2004). According to this definition, all cases not meeting criteria for category I or II SIDS, including those for which an autopsy has not been performed, are now called "Unclassified Sudden Infant Death" (Krous et al. 2004). To also include cases of sudden unexpected death attributed to positional suffocation (previously often classified as SIDS), in 2010 the Centers for Disease Control (CDC) introduced the term "sudden unexpected infant death (SUID)," which includes SIDS, ill-defined and unknown causes of death, and accidental sleep-related suffocation (Shapiro-Mendoza et al. 2014). In an initial evaluation of this classification system, 88% of 436 SUID were classified as unexplained, with 73% occurring in an unsafe sleep environment, while 12% were assigned to suffocation, and 22% to possible suffocation with unsafe sleep factors. With the increased recognition of positional suffocation as a potential cause of death, it seems important from an epidemiological and preventive point of view not to dismiss cases that previously had been classified as SIDS, but now as suffocation (Malloy and MacDorman 2005).

66.3.1 Epidemiology

66.3.1.1 Incidence

Despite a recent decline in incidence, SIDS continues to be the leading cause of postneonatal mortality in developed countries after excluding perinatal event-related deaths (Table 2). Because of the misclassification problem mentioned above, it is important always to report changes in both SIDS and postneonatal mortality rates and to uniformly use a classification system that includes SIDS and deaths ascribed to accidental suffocation, such as that introduced by the CDC (see above).

66.3.1.2 Age and Time of Death

One of the most striking epidemiological features in SIDS is its characteristic age distribution. Some 75% of deaths occur between 2 and 4 months of age, and 95% before 9 months of age (Poets 2008). Early beliefs that SIDS is extremely rare in the neonatal period cannot be maintained: 6–7% of SIDS victims are younger than 1 month of age, and 11% of all neonatal deaths are due to SIDS (Poets 2008). There is also the recent recognition that sudden deaths or near-death events may occur in apparently healthy neonates only a few hours after delivery. Here, many risk factors otherwise largely abandoned in recent years (see below), such as prone position, overheating, or maternal fatigue, continue to be highly prevalent. Caregivers need to be alerted to the possibility of these events to occur

Table 2 SIDS and postneonatal mortality (PNM) rates in different countries, 1990 vs. 2003 (Data taken from Hauck FR, Tanabe KW: International Trends in Sudden Infant Death Syndrome: Stabilization of rates requires further action. Pediatrics 2007; 122:660–666)

Country	PNM1990	PNM2003	Change(%)	SIDS1990	SIDS2003	Change(%)
Netherlands	2.3	1.2	−48	0.56	0.10	−82
Sweden	2.4	0.96	−60	1.0	0.23	−77
Germany	3.3	1.4	−58	1.42	0.43	−70
USA	3.38	2.67	−31	1.30	0.54	−58
New Zealand	4.21	1.90	−55	2.90	0.80	−72

and infants closely monitored already in the delivery room (Poets et al. 2012).

Throughout the year, there used to be a preponderance of the cold season, but this has almost disappeared following the back-to-sleep campaigns.

66.3.1.3 Risk Factors

A large number of factors associated with an increased risk of SIDS have been identified (Poets 2008) (Table 3). Many underscore the importance of social factors in the pathogenesis of SIDS; others, such as maternal smoking or anemia during pregnancy, suggest that there must already be a disturbance during intrauterine life that poses an infant at risk. Factors that are potentially amenable to modification include maternal smoking, not breast feeding, not using a pacifier, overheating, and a nonsupine sleep position, and these are the factors targeted by most intervention campaigns. Subsequently, however, additional modifiable risk factors have been identified. These include head covering, which has a pooled adjusted OR of 16.9 (95% CI 13.6; 22.7) and a population-attributable risk (PAR) of 27% (Blair et al. 2008), and prone sleeping in preterm and low birth weight infants. Parents of the latter infants may get confused by the common use of the prone position in hospital; it is thus particularly important to place these infants on their back before hospital discharge and to explain the importance of supine sleeping to their parents. Bed-sharing is also a relatively "new" risk factor. This practice seems particularly dangerous if taking place on a sofa or with a parent who drank alcohol or who smokes and cosleeps with an infant <3 months of age (Blair et al. 2014).

Table 3 Risk factors for SIDS (Derived from Poets (2008) with permission)

Maternal factors	Infantile factors
Young age	Male gender
Multiparity	Low birth weight
Smoking during pregnancy	Low birth length
Maternal drug abuse	Premature birth
Previous fetal deaths	Blood type B
Anemia during pregnancy	Low Apgar scores
Placenta praevia	Low hematocrit at 48 h
Premature rupture of membranes	Not using a pacifier
Low social class	Prone or side sleeping position
Low family income	Bed-sharing
Short interpregnancy interval	Overheating
Unmarried mother	Not breastfed
Partner unemployed	Siblings in family
Late attendance of antenatal clinic	Sleeping in own room
Postnatal depression	Previous SIDS in family
Attendance to psychiatrist	Previous cyanotic episode
Urinary tract infection in pregnancy	

66.3.2 Pathology

66.3.2.1 Intrathoracic Petechial Hemorrhages

As implied by its definition, there is no morphological finding in SIDS that sufficiently explains death. There are, however, a number of characteristic findings in these infants, such as serosal petechiae, which are so consistent that they appear to support the concept that SIDS may indeed form a specific disease entity. Other characteristic findings in SIDS include the occurrence of (often bloody) froth around the nose and mouth. Both may result from high transpulmonary pressure swings, such as occurring during breathing against an obstructed upper airway (Poets 2008).

66.3.2.2 Abnormalities in Brainstem Serotonergic System

Serotonin is a neurotransmitter involved in regulating various processes potentially related to SIDS, e.g., sleep and arousal, control of breathing, airway reflexes, and autonomic function (Paterson et al. 2007). Endogenously released serotonin is also required for gasping. Comparative studies on the binding properties of neurotransmitter receptors found multiple brainstem abnormalities in SIDS compared to control infants, suggesting

that such abnormalities may be involved in some SIDS deaths (Paterson et al. 2007).

66.3.3 Genetic Studies in SIDS

Some infants who die suddenly and unexpectedly do so because they have an inherited disease such as the A984G mutation in the medium-chain acyl-CoA dehydrogenase (MCAD) gene or in genes encoding cardiac ion channels resulting in long-QT syndrome. These well-defined diseases, however, contribute only a few percent to all cases of SIDS (and, by definition, prohibit defining SIDS as the cause of death). More relevant to SIDS may be recent data on gene polymorphisms that may predispose infants to SIDS under certain circumstances, such as those found in the serotonin transporter gene, although there are also strong arguments to question this proposed link (Paterson et al. 2007; Weese-Mayer et al. 2007; Paterson 2013).

66.3.4 Pathophysiology

There are now a number of recordings from cardiorespiratory monitors that were obtained during SIDS. Despite some limitations, these recordings have for the first time provided us with objective data on the pathophysiological mechanisms immediately preceding SIDS. In an analysis of nine recordings of chest wall impedance and heart rate from infants who had an autopsy diagnosis of SIDS or mild BPD, gasping was the predominant pattern, being already present at the time of the monitor alarm in three infants and occurring within 3 min after it in a further four (Fig. 2) (Poets et al. 1999b). Primary trigger for the monitor alarm had been bradycardia in all but two infants, but there was no indication of heart block or ventricular tachycardia. These observations, confirmed by a similar, more recent study (Sridhar et al. 2003), suggest that prolonged apnea is unlikely to be a primary mechanism in the sequence of events leading to most cases of SIDS, while the "primary" bradycardia is most likely caused by hypoxemia. In addition, there seems to be a failure or depression of arousal and gasping. The underlying causes of both the hypoxemia and the failure of these infants to resuscitate themselves from this hypoxemia remain to be determined.

66.3.5 Prevention

66.3.5.1 Primary Prevention

Dissemination of advice on safe sleeping has been one of the most effective health interventions ever performed. Recommendations are reviewed in regular intervals to incorporate new data. The current advice given by the American Academy of Pediatrics (AAP) includes the following (abbreviated) (American Academy of Pediatrics 2011):

- Infants should be placed for sleep in a supine position for every sleep.
- Use a firm sleep surface. Pillows or sheepskins should not be placed under a sleeping infant.
- Room-sharing without bed-sharing is recommended.
- Keep soft objects and loose bedding out of the crib.
- Pregnant women should receive regular prenatal care.
- Avoid smoke exposure during pregnancy and after birth.
- Avoid alcohol and illicit drug use during pregnancy and after birth.
- Breastfeeding is recommended.
- Consider offering a pacifier at nap time and bedtime.
- Avoid overheating. Bedroom temperature should be comfortable for a lightly closed adult.
- Do not use home cardiorespiratory monitors as a strategy for reducing the risk of SIDS.
- Infants should be immunized in accordance with recommendations of the AAP and CDC.
- Avoid commercial devices marketed to reduce the risk of SIDS.
- Supervised, awake tummy time is recommended to facilitate development and to minimize development of positional plagiocephaly.

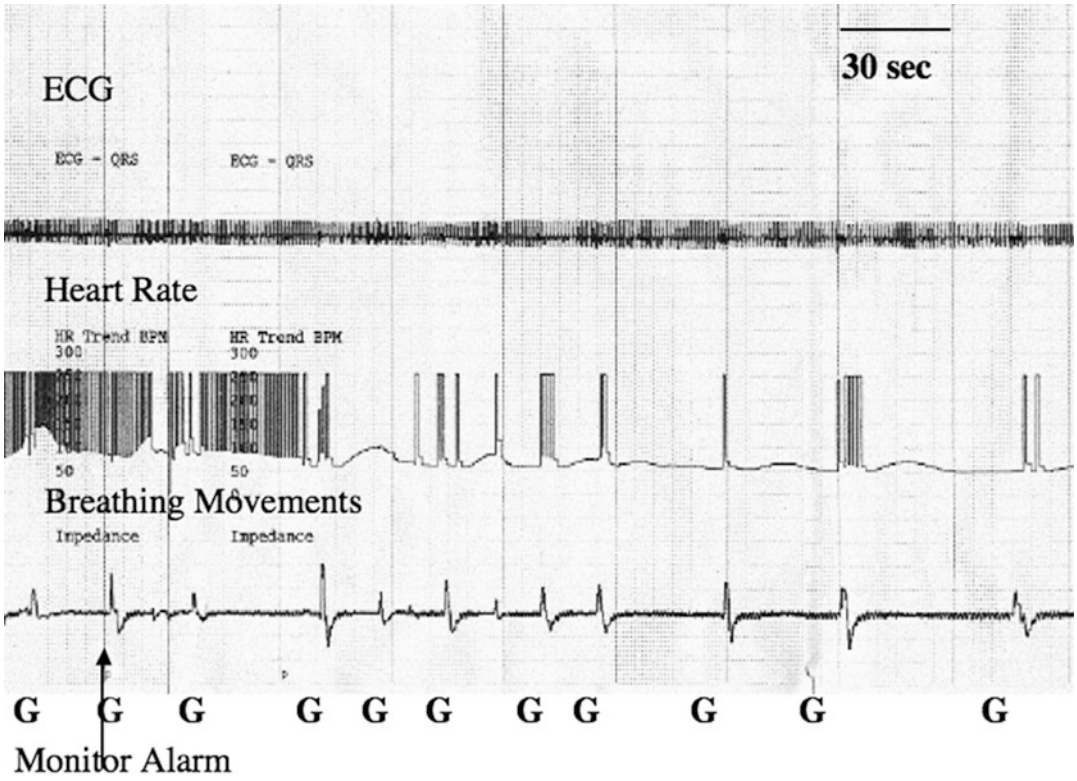

Fig. 2 Section from a memory monitor printout of a 1-month old infant born at 34 weeks gestation and with an autopsy diagnosis of SIDS. There are 11 gasps which progressively decrease in amplitude. There is an increase in heart rate from 72 to 140 bpm during the first 20 s of recording, followed by several smaller increases in heart rate that appear to occur in response to the gasps and are also decreasing in amplitude over time (From Poets et al. (1999b), with permission). G, gasp

66.3.5.2 Secondary Prevention

For many years, the use of home monitors in specific risk groups, i.e., secondary prevention, has been the only method to prevent SIDS, but its effectiveness in reducing its incidence has never been proven, and the AAP now clearly discourages its use to prevent SIDS. Nonetheless, home monitoring may be prescribed as a diagnostic tool or as an early warning of potentially dangerous pathophysiology. The first indication comprises infants after an apparent life-threatening event (ALTE) and infants from families who had two or more sudden unexpected infant deaths. Here, documented monitoring may help to reach a diagnosis. A detailed description of the diagnostic work-up of infants with ALTE would go beyond the scope of this chapter; the reader is referred to a recent Clinical Practice Guideline (Tieder et al. 2016). The second group involves technology-dependent infants (e.g., with a tracheostomy), infants with respiratory control disorders, and preterm infants with persistent AOP. AOP is not associated with an increased risk of SIDS, but monitoring may be indicated to prevent potential sequelae of IH (see above). Whatever the indication, a pulse oximeter with motion-resistant technology to reduce the frequency of false alarms is currently the preferred monitoring device. Although there are no controlled trials on this issue, there is evidence to suggest that apnea and hypoxemia may occur too late during the events leading to death always to allow for successful resuscitation. Monitoring should continue for 4 weeks after the last (true)

monitor alarm except for siblings from families with multiple deaths who should be monitored until the age of the oldest infant who died.

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