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In most situations, especially those requiring short term ventilation, discontinuing mechanical ventilation is not too challenging. This process, however, becomes more difficult when dealing with very premature and extremely low birth weight babies as well as those recovering from major respiratory failure, who required prolonged ventilatory support. The process of discontinuing mechanical ventilation in such babies has become a major clinical challenge and constitutes a large proportion of the workload in most neonatal intensive care units.

CASE STUDY 1

Baby MM was born by normal vaginal delivery at 25 weeks' gestation with a birth weight of 890 g. Mother had received two doses of antenatal steroid. Her membranes had ruptured four days before delivery. The baby's condition at birth was satisfactory but he was immediately intubated and given prophylactic surfactant. However, he did develop respiratory failure due to hyaline membrane disease and required mechanical ventilation. On day 2, he was commenced on total parenteral nutrition (TPN) and enteral feeds were slowly introduced. On day 7, he developed features of necrotising enterocolitis for which he received conservative treatment for seven days. On day 18, he was noted to have signs of patent ductus arteriosus (PDA) which was treated with a course of indomethacin. Despite this, he needed an increased level of ventilatory support to maintain adequate gas exchange. A repeat echocardiography revealed persistence of a haemodynamically significant PDA which needed surgical ligation on day 26. The immediate postoperative course was complicated with development of pulmonary hypertension which responded quickly to inhaled nitric oxide treatment. However, he remained ventilator dependent and by day 28 was showing signs of chronic lung disease. For this, he was commenced on a 10 day course of dexamethasone (a total dose of 712 µg/kg over 10 days; DART (dexamethasone: a randomized trial), bronchopulmonary dysplasia (BPD) regimen¹). On day 34, he was extubated to nasal prong continuous positive airway pressure (CPAP) at 6 cm of water which he tolerated well. After a week, he was weaned off CPAP but still required low flow oxygen via nasal cannula for a further 19 days. Since then he remained well in air.

CASE STUDY 2

Baby ZU was born at 31 weeks' gestation with a birth weight of 1.56 kg after uneventful pregnancy. He was ventilated for respiratory distress syndrome at moderate settings and received one dose of surfactant. He was extubated on day 5 but this lasted for only three hours as he developed a stridor and required re-intubation. Subsequently, he failed five extubation attempts despite two short courses of peri-extubation dexamethasone (200 µg/kg, three doses at eight hourly interval). Bronchoscopy showed no evidence of collapse or compression of the airways. A high resolution computed tomographic (CT) scan of the chest showed patchy areas of lung density on both sides, thought to be related to inflammatory reaction which was treated with antibiotics. Bedside monitoring of pulmonary mechanics did not show any specific abnormality.

Various modes of synchronised mechanical ventilation, including volume and pressure targeted modes using continuous and variable flow, and pressure support, were used to facilitate weaning without success. A wide variety of diagnostic tests were also performed to investigate the cause of his repeated failure of extubation such as karyotyping and tests for neuromuscular diseases including muscle enzymes, nerve conduction velocity, electromyogram (EMG) and muscle biopsy, which were all normal. The cranial ultrasound and magnetic resonance imaging of the brain did not show any abnormality. Polymerase chain reaction (PCR) analysis of the PHOX2B gene for congenital central hypoventilation syndrome (CCHS) was normal. In absence of a diagnosis and need for prolonged respiratory support, a tracheostomy was performed. He was ventilated for another week and subsequently weaned to CPAP through a tracheostomy tube.

PHYSIOLOGIC CONSIDERATIONS

Successful weaning and extubation is dependent upon a balance between adequacy of pulmonary gas exchange and performance of the respiratory muscle pump.² Failure of the respiratory muscle

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Table 1 Possible causes of difficult weaning and failure of extubation

Increased respiratory load	Reduced respiratory capacity
<i>Increased elastic load</i>	<i>Decreased respiratory drive</i>
<ul style="list-style-type: none"> ▶ Unresolved lung disease ▶ Secondary pneumonia ▶ Left to right shunt (PDA) ▶ Abdominal distension ▶ Hyperinflated lungs 	<ul style="list-style-type: none"> ▶ Excessive sedation ▶ CNS infection ▶ Brain lesions such as PVH and PVL ▶ Hypocapnea/alkalosis
<i>Increased resistive load</i>	<i>Muscular dysfunction</i>
<ul style="list-style-type: none"> ▶ Thick/copious airway secretions ▶ Narrow/occluded endotracheal tube ▶ Upper airway obstruction 	<ul style="list-style-type: none"> ▶ Muscular weakness (malnutrition) ▶ Severe electrolyte disturbances ▶ Chronic pulmonary hyperinflation (BPD)
<i>Increased minute ventilation</i>	<i>Neuromuscular disorders</i>
<ul style="list-style-type: none"> ▶ Pain and irritability ▶ Sepsis/hyperthermia ▶ Metabolic acidosis 	<ul style="list-style-type: none"> ▶ Diaphragmatic dysfunction ▶ Prolonged neuromuscular blockage (in renal failure, concomitant use of aminoglycoside and phenobarbitone) ▶ Myotonic dystrophy/spinal muscular atrophy/other myopathies ▶ Cervical spinal injury

BPD, bronchopulmonary dysplasia; CNS, central nervous system; PDA, patent ductus arteriosus; PVH, periventricular haemorrhage; PVL, periventricular leucomalacia.

pump is probably the most common cause of the inability to wean from mechanical ventilation. Intolerance of extubation may therefore be the result of either increased *load* on the respiratory muscles, and/or decreased inspiratory drive and endurance (capacity).³ The management of such infants requires the identification and correction of all factors that have the potential to impede the tolerance for spontaneous breathing (table 1). Moreover, weaning from mechanical ventilation is a dynamic process and is influenced, particularly in newborns, by many factors such as differing stages of lung development, changing status of the underlying lung disease, secondary complications, a unique interaction of the neonatal heart and lungs, and the relation between central control of respiratory drive and respiratory muscles.

HOW TO WEAN?

The classic approach to weaning from conventional ventilation is to extubate from low rate intermittent mandatory ventilation (IMV), either directly to supplemental oxygen or CPAP. Weaning during newer modes of ventilation such as synchronised ventilation, however, is conceptually different than it has been for conventional IMV, because many of the parameters previously set by the clinician are now patient

controlled, particularly during patient triggered (assist control) ventilation⁴⁻⁵ (table 2). During patient triggered ventilation, as long as the baby is breathing above the control (back up) rate, reduction in the rate brings about no change in ventilator cycling or support (fig 1). Moreover, because the infant is setting his or her own inspiratory time (in flow cycling), the inspiratory–expiratory ratio cannot be changed. Thus, reduction in peak inspiratory pressure is the primary manoeuvre. Weaning methods in synchronised IMV (SIMV) are similar to IMV—that is, weaning is achieved by decreasing the SIMV rate and peak inspiratory pressure (PIP). However, one should avoid using a very low SIMV rate and attempt to maintain a minimum but adequate tidal volume delivery (3–4 ml/kg). If babies require continuing minimal support through SIMV, an alternative approach is to use pressure support ventilation (PSV) in conjunction with SIMV. The major function of PSV is to assist respiratory muscle activity and thus reduce the workload. PSV is intended to give the patient an inspiratory pressure “boost” during spontaneous breathing so as to overcome the imposed work of breathing created by the endotracheal tube, demand valve, and ventilator circuit. However, because it is pressure limited, tidal volume delivery in PSV depends on respiratory mechanics and thus may be variable. To overcome this variability, some devices have now combined pressure support with a guaranteed tidal volume delivery, such as volume assured pressure support (VAPS).⁶ Another promising ventilatory strategy is proportional assist ventilation (PAV), in which the ventilator generates pressure proportional to the patient’s effort.⁷ The more the patient “pulls”, the more pressure the machine generates. To do so, the ventilator must be able to sense or estimate patient effort on an ongoing basis. This property makes PAV a potentially useful mode for weaning infants from mechanical ventilation. Although the clinical application of high frequency ventilation (HFV) is well described in the literature, there is no consensus as to whether extubation directly from very low HFV settings to either no support or CPAP offers any advantages over switching directly to conventional ventilation. The weaning strategies related to specific modes of ventilation are summarised in table 3.

DIFFICULT WEANING

Commonly, more than one factor is responsible for weaning failure (table 1). The management of such infants requires the identification and correction of all factors that have the potential to impede tolerance of spontaneous breathing. Careful strategy including choice of ventilatory modes and appropriate setting of the ventilatory parameters to match the underlying pathophysiology should be an important consideration in such cases. For example, PSV may be an effective mode of ventilation in conditions with increased expiratory resistance such as BPD, and similar adjustment in ventilator inspiratory flow might help to reduce the patient’s work of breathing during mechanical ventilation. The maintenance of minute ventilation in a range sufficient to assure adequate removal of carbon dioxide is essential. For the healthy newborn, a tidal volume of 4–6 ml/kg and a respiratory rate of 40–60 breaths/min suggests that the minute ventilation should be approximately 240–360 ml/kg/min in infants with normal lungs.⁸ It may be inferred that alveolar hypoventilation will occur if either tidal volume or the respiratory rate is too low. Where available, monitoring of pulmonary function and mechanics might be useful to gain

Table 2 Level of patient control in various modes of triggered ventilation

	IMV	SIMV	ACV	PSV
Trigger	Ventilator	Patient	Patient	Patient
Rate	Ventilator	Ventilator	Patient	Patient
Inspiratory time	Ventilator	Ventilator	Ventilator	Patient

ACV, assist control ventilation; IMV, intermittent mandatory ventilation; PSV, pressure support ventilation; SIMV, synchronised intermittent mandatory ventilation.

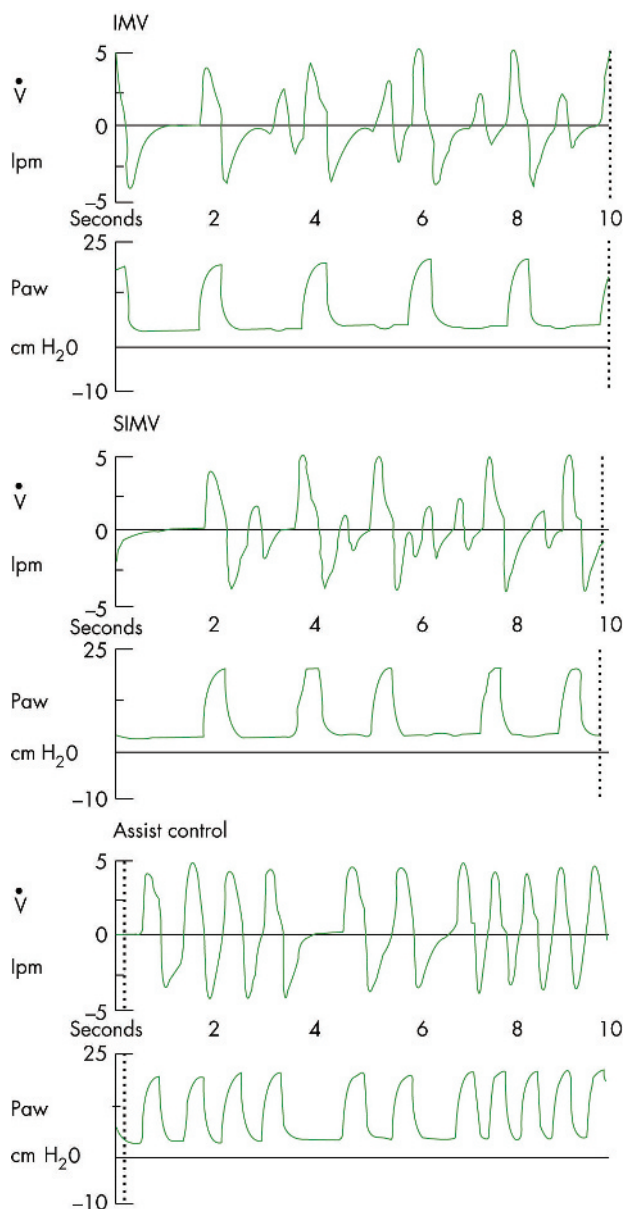


Figure 1 Flow and pressure waveforms for intermittent mandatory ventilation (IMV), synchronised intermittent mandatory ventilation (SIMV), and assist-control ventilation (A/C). During IMV (top), note mechanical breaths (larger flow waveforms) delivered at fixed intervals, set by the clinician. Spontaneous breaths may occur between mechanical breaths, but may not generate significant positive pressure. During SIMV (middle), spontaneous patient effort above a set threshold can trigger a mechanical breath if it occurs within a "timing window". Thus, mechanical breaths occur at a slightly variable interval. Spontaneous breaths between timing windows do not result in triggering and do not generate effective pressure. During assist control (A/C, bottom) each spontaneous breath which exceeds the trigger threshold is augmented by machine delivered breath. Thus each breath is identical. The rate will vary according to the patient's own rate, but will not fall below the control back-up rate set by the clinician. Reproduced with permission from Sinha and Donn.³⁴

some insight into the reasons for ventilatory dependency in an individual baby.⁹ There have been only a few randomised trials which have compared the effect of newer techniques of ventilation primarily on weaning. Most published studies designed to look into the safety and efficacy of these newer modes have included "duration of ventilation" only as an

Table 3 Suggested weaning strategies related to commonly used newer modes of ventilation

Modes of ventilation	Weaning strategies
1. A/C	Decrease PIP but provide adequate V_T (≥ 4 ml/kg) Decrease back up rate to 25–30 May increase trigger sensitivity to condition respiratory muscles
2. SIMV	Extubate directly from assist control or switch to SIMV Decrease rate Decrease PIP but provide adequate V_T (≥ 4 ml/kg) Extubate when stable at low rate (i.e. 15 breaths/min) or combine with PSV
3. SIMV/PSV	Add PSV when SIMV rate below 30/minute Adjust level of PSV to give adequate V_T (≥ 4 ml/kg) Reduce SIMV slowly Extubate when stable at low SIMV rate (i.e. 15 breaths/min)
4. HFOV	Decrease both mean airway pressure and amplitude As the patient improves, and as amplitude decreases, the patient will do more spontaneous breathing When achieving most of the CO_2 elimination with spontaneous breathing, and the mean airway pressure has decreased sufficiently ($< 7\text{--}8$ cm H_2O and FiO_2 0.25–0.3), patient can be extubated

A/C, assist control (also known as PTV, patient triggered ventilation); FiO_2 , fraction of inspired oxygen; HFOV, high frequency oscillatory ventilation; PIP, peak inspiratory pressure; PSV, pressure support ventilation; SIMV, synchronised intermittent mandatory ventilation; V_T , tidal volume.

incidental parameter or surrogate outcome measure of ventilation.¹⁰ Similarly, in a recently published meta-analysis, volume controlled ventilation has been shown to be associated with reduced duration of ventilation and reduced incidence of pneumothorax as compared to traditional time cycled pressure limited (TCPL) ventilation.¹¹ Finally, the nutritional aspects of weaning, particularly in extremely low birth weight babies, cannot be overlooked, and efforts to provide an adequate energy intake to prevent catabolism might help to prevent weaning failure.

PHARMACOLOGICAL ADJUNCTS TO WEANING

Routine administration of corticosteroids and methylxanthines has been a common practice to help weaning and extubation, particularly in ventilator dependent babies. The practice of giving corticosteroids, mainly dexamethasone, falls into two main groups: (1) peri-extubation corticosteroid treatment in infants at increased risk for airway oedema and obstruction, such as those who have received repeated or prolonged intubation¹²; (2) postnatal corticosteroid treatment as a strategy to prevent chronic lung disease, which coincidentally reduces the duration of intubation and ventilation.^{13–16} However, concerns were raised about the potential hazards of corticosteroid treatment on the developing central nervous system and lungs.¹⁷ This concern had led to its restricted use even in some chronically ventilated babies who might have otherwise benefited from its use. This was shown in a recently published systematic review which confirmed that the effect of postnatal corticosteroids on the combined outcome of death or cerebral palsy varies with the level of risk for chronic lung disease.¹⁸ From the published data it seems that treatment between 7–14 days of age in chronically ventilated infants using a much lower dose and restricting its use for a maximum of 7–10 days might give best outcomes.^{19 20}

Methylxanthines (theophylline and caffeine) have also been used for a long time because of their many theoretical advantages, including increased central respiratory drive and increased diaphragmatic contractility and endurance.²¹ However, like dexamethasone, there have been concerns about ischaemic brain injury because of antagonistic properties against adenosine receptors.²² A large international multicentred trial to examine the safety and efficacy of caffeine is underway; the preliminary results on about 2000 babies enrolled in this study show a pronounced beneficial effect on many clinically relevant end points including significant reduction in duration of ventilation and incidence of BPD.²³ Other pharmacologic agents often used to facilitate the process of weaning are diuretics and bronchodilators. Like steroids, they have been used as a strategy for treatment of chronic lung disease and have been shown to be beneficial in improving lung function in specific situations, but there are not enough data to recommend their routine use for weaning.

PREDICTIVE INDICES

Attempts have been made to devise some objective parameters which might be used as an adjunct to clinical decision making to facilitate extubation. These “predictive” indices assess different physiologic functions of the respiratory system, including the effect of spontaneous breathing and respiratory muscle endurance (table 4).^{24–33} However, despite having potential for clinical applicability, these tools still remain mostly investigative in nature and do not provide a “threshold” value for either individual or a combination of measurements that would consistently discriminate between success and failure of extubation.³¹

CLINICAL RELEVANCE OF CASE STUDIES

Case 1 is typical of a preterm infant whose course of mechanical ventilation is complicated by problems related to parenchymal lung injury and haemodynamic compromise secondary to ductal shunting. Efforts to wean included attention to maintaining alveolar inflation in the face of pulmonary oedema and eliminating the patency of the ductus arteriosus. This could not be accomplished pharmacologically, but after surgical ligation it became possible to continuously wean the baby and eventually extubate him.

Extubation in babies receiving mechanical ventilation: key points

- ▶ Successful weaning and extubation is dependent on a balance between the respiratory load and respiratory capacity
- ▶ Repeated failure to wean suggests incomplete resolution of the underlying condition, other impediments to weaning, or poor endurance
- ▶ The methods of weaning with newer styles of ventilation are specific to individual modes and require familiarity
- ▶ Use of on-line pulmonary mechanics testing and graphics may improve clinical decision making process regarding weaning and extubation
- ▶ The weaning and extubation should always be a planned process, taking into account various clinical and physiological considerations specific to the individual baby

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Case 2 is less common. It represents a situation in which lung parenchyma and airways are normal, but respiratory effort is severely hampered either due to some neuromuscular incompetence or lack of central drive. Weaning is facilitated by recognising that the baby is capable of normal gas exchange as long as lung expansion is facilitated by mechanical ventilation. All tests for neuromuscular dysfunction in this were normal and this baby did not carry the congenital central hypoventilation syndrome (CCHS) polyalanine repeat expansion mutation. A small percentage of cases with CCHS may have alternative mutations in PHOX2B which might not have been identified in this assay. Some cases may have symptoms of CCHS but no mutation of the above gene. They may represent phenocopies with mutation in different genes or may have a different disease process. Tracheostomy is necessary when very long term assisted ventilation is contemplated.

WAY FORWARD

Weaning infants from mechanical ventilation involves as much “art” as “science” and should be planned according to clearly defined clinical and physiologic goals. The measurement of pulmonary mechanics and lung volumes, now available at the bedside, might help in gauging the capacity for weaning, even though its clinical usefulness has not been

Table 4 Clinical trials of predictive indices in weaning

Physiologic parameters	Indices	Comments
Pulmonary mechanics ^{23 24}	<ul style="list-style-type: none"> ▶ Lung compliance (C_{RS}) (ml/cmH₂O/kg) ▶ Lung resistance (R_{RS}) (cm/H₂O/l/s) 	<ul style="list-style-type: none"> ▶ Equivocal results ▶ Poor discriminatory value of individual indices
Pulmonary function ²⁵	<ul style="list-style-type: none"> ▶ Resistive work of breathing (g×cm/kg) ▶ Functional residual capacity (FRC) (ml/kg) 	<ul style="list-style-type: none"> ▶ Uncontrolled studies with fewer numbers ▶ Measurement made after extubation ▶ Threshold value <26 ml/kg for failure; sensitivity 71%, specificity 77%
Effect of breathing and respiratory muscle endurance ^{26–30}	<ul style="list-style-type: none"> ▶ Spontaneous breath tidal volume (ml/kg) ▶ Minute ventilation (ml/min/kg) (ratio of spontaneous: mechanical breaths) ▶ Mean inspiratory flow (V_T/TT) ▶ Inspiratory pressure/maximal inspiratory pressure (PI/Plmax) 	<ul style="list-style-type: none"> ▶ Not discriminatory ▶ Positive predictive value 86% but requires controlled study ▶ Methodological inconsistency ▶ Different “threshold” values
Composite data ^{31 32} (integrated indices)	<ul style="list-style-type: none"> ▶ Respiratory frequency and tidal volume ratio (f/V_T breaths/min/l) ▶ CROP index (compliance, rate, oxygenation and pressure) 	<ul style="list-style-type: none"> ▶ Not assessed in homogenous neonatal population ▶ Not discriminatory as in adults

PI, inspiratory pressure; Pl_{MAX}, maximal inspiratory pressure; TT, inspiratory time; V_T, tidal volume.

confirmed in controlled trials. Similarly methods that will rapidly and reliably assesses and predict infant's readiness for extubation would provide clinicians a useful adjunct to their clinical decision making for extubation, and additional clinical investigation in this area is very much needed. Given the availability and variety of newer ventilatory modes that were not available previously, clinicians now have a choice of different weaning techniques which is becoming more extensive every day and they have an obligation to harness all of this new "power" wisely. The evidence base is as yet not established for most of these techniques, but the time is right to organise well randomised clinical trials to answer the myriad of questions that the new technologies have raised.

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REFERENCES

- Neonatal Formulary**. The Northern Neonatal Network. London: BMJ Publishing Group, 2003:91.
- Harris TR**, Wood BR. Physiologic principles. In: Goldsmith JP, Karotkin EH, eds. *Assisted ventilation of the neonate*, 4th ed. Philadelphia: WB Saunders Co, 2003:21–68.
- Lessard MR**, Bronchard LJ. Weaning from ventilatory support. *Clinics in Chest Medicine* 1996;**17**:475–89.
- Donn SM**, Sinha SK. Newer modes of mechanical ventilation for the neonate. *Current Opinion in Paediatrics* 2001;**13**:99–103.
- Greenough A**. Update on modalities of mechanical ventilation. *Arch Dis Child Fetal Neonatal Ed* 2002;**87**:F3–6.
- Sinha SK**, Donn SM. Volume-controlled ventilation. Variation on a theme. *Clin Perinatal* 2001;**28**:547–60.
- Schulze A**, Gerhardt T, Musante G, et al. Proportional assist ventilation in low birth weight infants with acute respiratory disease. A comparison to assist-control and conventional mechanical ventilation. *J Pediatr* 1999;**135**:339–44.
- Abbasi S**, Sivieri EM, Bhutani VK. Evaluation of pulmonary function in the neonate. In: Polin RA, Fox WW, Abman SH, eds. *Fetal and neonatal physiology*, 3rd ed. Philadelphia: WB Saunders, 2003:1919–25.
- Sinha SK**, Nicks JJ, Donn SM. Graphic analysis of pulmonary mechanics in neonates receiving assisted ventilation. *Arch Dis Child Fetal Neonatal Ed* 1996;**75**:F213–18.
- Greenough A**, Milner AD, Dimitriou G. Synchronized mechanical ventilation for respiratory support in newborn infants. *The Cochrane Database of Systematic Reviews*, 2004, Issue 3. Art No. CD000456.
- McCallion N**, Davis PG, Morley CJ. Volume-targeted versus pressure-limited ventilation in the neonate. *The Cochrane Database of Systematic Reviews*, 2005, Issue 3. Art. No. CD003666.
- Davis PB**, Henderson-Smart DJ. Intravenous dexamethasone for extubation of newborn infants (Cochrane Review). In: *The Cochrane Library*, Issue 1. Oxford: Update Software, 1999.
- Kovacs I**, Davis GM, Faucher D, et al. Efficacy of sequential early systemic and inhaled corticosteroid therapy in the prevention of chronic lung disease of prematurity. *Acta Paediatr* 1998;**87**:792–8.
- Papile LA**, Tyson JE, Stoll BJ, et al. A multicenter trial of two dexamethasone regimens in ventilator dependent premature infants. *N Engl J Med* 1998;**338**:1112–18.
- Bhutta T**, Ohlsson A. Systematic review and meta-analysis of early postnatal dexamethasone for prevention of chronic lung disease. *Arch Dis Child Fetal Neonatal Ed* 1998;**79**:F26–33.
- Halliday HL**, Ehrenkranz RA. Early postnatal (<96 hours) corticosteroids for preventing chronic lung disease in preterm infants (Cochrane Review). In: *The Cochrane Library*, Issue 1. Oxford: Update Software, 1999.
- Barrington KJ**. The adverse neuro-developmental effects of postnatal steroids in the preterm infant: a systematic review of RCTs. *BMC Pediatr* 2001;**1**:1.
- Doyle LW**, Halliday HL, Ehrenkranz RA. Impact of postnatal systemic corticosteroids on mortality and cerebral palsy in preterm infants: effect modification by risk for chronic lung disease. *Pediatrics* 2005;**115**:655–61.
- Halliday HL**, Ehrenkranz RA. Moderately early (7–14 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants (Cochrane Review). In: *The Cochrane Library*, Issue 1. Oxford: Update Software, 1999.
- Neonatal Formulary**. The Northern Neonatal Network. London: BMJ Publishing Group, 2000.
- Laubscher B**, Greenough A, Dimitriou G. Comparison effects of theophylline and caffeine on respiratory function of prematurely born infants. *Early Hum Dev* 1998;**50**:185–92.
- Dux E**, Fastbom J, Ungerstedt U, et al. Protective effect of adenosine and a novel xanthine derivative propentofylline on the cell damage after bilateral carotid occlusion in the gerbil hippocampus. *Brain Res* 1990;**516**:248–56.
- Schmidt B**, Roberts R, Davis P, et al for the CAP Investigators. Efficacy and safety of methylxanthines in very low birth weight (VLBW) infants: preliminary results from the international caffeine for apnoea of prematurity (CAP). Washington: Presented at Pediatric Academic Society meeting, 2005.
- Balsan MJ**, Jones JG, Watchko JF, et al. Measurements of pulmonary mechanics prior to the elective extubation of neonates. *Pediatric Pulmonology* 1990;**9**:238–43.
- Veness-Meehan KA**, Richter S, Davis JM. Pulmonary function testing prior to extubation in infants with respiratory distress syndrome. *Paediatric Pulmonology* 1990;**9**:2–6.
- Dimitriou G**, Greenough A, Laubscher B. Lung volume measurements immediately after extubation by prediction of 'extubation failure' in premature infants. *Paediatric Pulmonology* 1996;**21**:250–4.
- Wilson BJ Jr**, Becker MA, Linton ME, et al. Spontaneous minute ventilation predicts readiness for extubation in mechanically ventilated preterm infants. *J Perinatal* 1998;**18**:436–9.
- Gillespie LM**, White SD, Sinha SK, et al. Usefulness of 'minute ventilation test' in predicting successful extubation in newborn infants: a randomised controlled trial. *J Perinatal* 2003;**23**:205–7.
- El-Khatib MF**, Baumeister B, Smith PG, et al. Inspiratory pressure/maximal inspiratory pressure: does it predict successful extubation in critically ill infants and children? *Intensive Care Med* 1996;**22**:264–8.
- Dimitriou G**, Greenough A, Endo A, et al. Prediction of extubation failure in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2002;**86**:F32–5.
- Khan N**, Brown A, Venkataraman St. Predictors of extubation success and failure in mechanically ventilated infants and children. *Crit Care Med* 1996;**24**:1568–79.
- Baumeister BI**, el-Khatib M, Smith PG, et al. Evaluation of predictors of weaning from mechanical ventilation in pediatric patients. *Pediatr Pulmonol* 1997;**24**:344–52.
- Farias JA**, Alia I, Retta A, et al. An evaluation of extubation failure predictors in mechanically ventilated infants and children. *Intensive Care Med* 2002;**28**:752–7.
- Sinha SK**, Donn SM. Weaning from assisted ventilation: art or science? *Arch Dis Child Fetal Neonatal Ed* 2000;**83**:F64–70.