Recent advances

Care of near term infants with respiratory failure

Keith J Barrington, Neil N Finer

Neonatology is a fairly young specialty and has dramatically improved outcomes for premature infants. How to care for infants born at or near term (after 34-35 weeks' gestation) who are experiencing life threatening respiratory failure has become an increasingly important issue. In near term infants hypoxia and persistent pulmonary hypertension of the newborn often complicate meconium aspiration, pneumonia, pulmonary hypoplasia, and hyaline membrane disease—diseases which until recently had a high mortality once the infant had become severely hypoxic. New techniques and treatments seem to be resulting in improved survival rates. These include extracorporeal membrane oxygenation, inhaled nitric oxide, administration of exogenous surfactant, high frequency ventilation, and, potentially, liquid ventilation.

Methods

We have included references that we believe are pivotal to recent advances in neonatology, most of them referring to randomised controlled trials. We ensured that all important randomised trials were included by performing a Medline search using the search engine Medvyl Medline Plus. We searched under the following terms:

- Subject heading—"infant *or* newborn"
- Publication type—"randomised controlled trials *or* controlled clinical trials"
- Keywords—"extracorporeal *or* nitric *or* liquid ventilation *or* surfactant *or* high frequency ventilation."

We then deleted references to trials in premature infants. We included all of the relevant randomised controlled trials of extracorporeal membrane oxygenation, high frequency ventilation, surfactant, and nitric oxide. There were no such trials available of liquid ventilation. We included other references that illustrated important issues, and these were retrieved from our own databases.

Extracorporeal membrane oxygenation

Neonatal extracorporeal membrane oxygenation entails the continuous circulation of blood from the patient through an extracorporeal circuit, where heparin and oxygen are added and carbon dioxide removed. Then the blood is warmed and reinjected to supply all of the patient's oxygen requirements. The technique was first used successfully in an adult in 1972

Summary points

Extracorporeal membrane oxygenation reduces mortality in near term infants who are critically ill
Inhaled nitric oxide improves oxygenation and reduces the need for extracorporeal membrane oxygenation

Exogenous surfactant treatment may be effective when surfactant has been inactivated or destroyed—for example, in meconium aspiration and pneumonia

High frequency ventilation may improve the removal of carbon dioxide in some patients with respiratory failure

Liquid ventilation may have a role in some infants, particularly those with pulmonary hypoplasia, but it requires further investigation

Outcomes in near term infants can be greatly improved by an approach that recognises the benefits of new therapeutic techniques

Division of Neonatology, Department of Paediatrics, University of California, San Diego, San Diego, CA 92103-8774, USA

Keith J Barrington, professor of paediatrics

Neil N Finer, professor of paediatrics

Correspondence to: Dr Barrington kbarrington@ucsd.edu

BMJ 1997;315:1215-8

and in a neonate in 1975. Two small prospective controlled trials showed substantially improved survival in near term infants with hypoxia.^{1 2}

To assess the severity of respiratory failure and hypoxia in infants receiving respiratory support many studies have made use of the oxygenation index. This index is calculated as fractional inspired oxygen multiplied by 100 multiplied by mean airway pressure (in cm H₂O) divided by arterial oxygen pressure (in mm Hg). An oxygen index persistently greater than 40 was previously considered to be predictive of a mortality of 80% with maximal conventional treatment.¹ Infants given extracorporeal membrane oxygenation have usually had oxygen indices of greater than 40 on more than one occasion in spite of maximal treatment, and, overall, experienced centres currently achieve survival rates of about 80%.³ A recent multicentre, national trial conducted in the United Kingdom confirmed that, despite advances in neonatal care, mortality remains at 59% once an infant has such a high oxygen index.⁴ This trial also confirmed that referral for extracorporeal

Fig 1 Venovenous extracorporeal membrane oxygenation showing double lumen catheter. Inflow is directed towards the tricuspid valve to try to minimise recirculation

ecial membrane oxygenation reduced mortality to 30% in near term newborn infants with hypoxia and an oxygen index of greater than 40. Once the oxygen index exceeded 60, the benefit of extracorporeal membrane oxygenation was less obvious, reinforcing the necessity of urgent referral for such treatment.

Venoarterial extracorporeal membrane oxygenation is being gradually replaced by a venovenous technique in most neonates since the development of double lumen catheters (fig 1).⁵ The catheter is placed in the right atrium and drains and reinjects the blood into the same chamber, thus requiring cannulation of only the right jugular vein and sparing the carotid artery. In cases of primary cardiac dysfunction a venoarterial technique is usually needed. Venovenous extracorporeal membrane oxygenation seems to have fewer complications and is faster.⁶ Newer techniques for extracorporeal gas exchange, such as the single lumen cannula push-pull method, known as AREC (assistance respiratoire extra-corporelle),⁷ provide effective support in smaller infants and are simpler to operate. Indeed, percutaneous cannulation has now been successfully performed in neonates and may possibly extend the indications for extracorporeal membrane oxygenation.

Recent data from the international registry show a decrease in the use of neonatal extracorporeal life support, presumably because other new treatments such as inhaled nitric oxide and exogenous surfactant have been introduced. Not all infants will respond to these new treatments. Infants with diaphragmatic hernia, for example, are unlikely to respond to nitric oxide, and they already have a poorer outcome than other patients receiving extracorporeal membrane oxygenation, their survival rate being 62% compared with 83% in infants without diaphragmatic hernias. However, without extracorporeal membrane oxygenation, infants with diaphragmatic hernia who develop clinically significant hypoxia have a high mortality. In the recent British trial all 17 of the qualifying infants

who were randomly allocated to the control group died (four of the 18 infants receiving extracorporeal membrane oxygenation survived).⁴

Nitric oxide

Nitric oxide is a physiological mediator of vascular tone. It is usually released by the vascular endothelium and diffuses into the immediately underlying vascular smooth muscle to mediate vasodilatation.⁸ When inhaled at low concentrations of less than 80 parts per million it has a direct effect on pulmonary vascular resistance⁹ and improves matching of ventilation and perfusion¹⁰ without systemic effect. When nitric oxide enters the bloodstream it reacts with haemoglobin and rapidly, and with extremely high affinity, forms nitrosylhaemoglobin, which degrades to methaemoglobin and nitrate. Preliminary studies have shown dramatic improvements in arterial oxygen pressure. In a recently completed large international multicentre randomised masked controlled trial, inhaled nitric oxide given to infants with an oxygen index of greater than 25 significantly reduced the combined end point of death or the need for extracorporeal membrane oxygenation from 64% to 46% (fig 2).¹¹ A parallel study in 53 infants with diaphragmatic hernia did not show any benefit from inhaled nitric oxide: indeed, outcome may have been worsened.¹² A meta-analysis of six randomised controlled trials¹¹⁻¹⁷ shows that about 50% of infants will have clinically significant increases in oxygen index within 60 minutes (fig 3).¹⁸

Although inhaled nitric oxide has been assumed to have no systemic effects, it prevents platelet aggregation and increases bleeding time in rabbits and adults.¹⁹ This potential for bleeding should be considered carefully, especially in preterm infants, in whom bleeding may be catastrophic. Furthermore, the lowest effective dose should be used. The North American nitric oxide study showed that few infants will respond at 80 parts per million if there is no clear response at 20 parts per million,¹¹ and data from adults with the adult respiratory distress syndrome²⁰ and from animal studies⁹ suggest that much lower concentrations (possibly

Fig 2 Relative risks (with 95% confidence intervals) of death or need for extracorporeal membrane oxygenation in randomised controlled trials of inhaled nitric oxide

Fig 3 Relative probabilities in randomised controlled trials that oxygenation will increase by 30 to 60 minutes after inhalation of nitric oxide. Values are relative risks (95% confidence intervals)

less than 1 part per million) may produce clinically significant vasodilatation.

Other vasodilators that have not yet been shown to have selective or clinically beneficial effects when given systemically are now being studied for use by inhalation. They include tolazoline and prostacyclin.²¹ The most appropriate drug would have a direct immediate effect on the pulmonary vasculature and be rapidly degraded by circulating enzymes to prevent systemic effects even after prolonged treatment. The vasodilating actions of prostacyclin are dependent on a receptor mediated increase in intracellular cyclic AMP.²² This suggests that there may be synergy with inhaled nitric oxide, whose actions are mediated through cyclic GMP. Combined treatment with inhaled nitric oxide and prostacyclin might therefore have even greater benefits.

Surfactant

Exogenous surfactant has been dramatically effective in reducing the death rate from respiratory distress in premature infants. Many of the respiratory diseases afflicting infants at term are also associated with abnormalities in surfactant metabolism. Meconium, for example, both displaces²³ and inactivates²⁴ surfactant, particularly by interfering with its protein function. Pneumonia is often associated with increased alveolar capillary permeability and inactivation of surfactant by fibrin in plasma.²⁵ Some organisms such as group B streptococcus seem to injure pulmonary epithelial cells directly.²⁶ Lungs that are hypoplastic, either in association with diaphragmatic hernia²⁷ or for other reasons,²⁸ also seem to have altered metabolism and reduced pools of surfactant, even after adjustment for the smaller size of the lung.

All common pulmonary disorders in near term newborn infants therefore seem to have substantially disturbed surfactant function. Surfactant treatment seems to produce short term benefits of improved oxygenation, improved lung mechanics, and decreased ventilatory requirements. One small randomised controlled trial in term infants with meconium aspiration showed a reduction in air leaks and in the need for

extracorporeal membrane oxygenation.²⁹ Infants already receiving extracorporeal membrane oxygenation for other reasons had shorter treatments and fewer complications after surfactant treatment compared with infants randomly allocated to a control group.³⁰ A randomised, controlled trial in infants with various types of hypoxaemic respiratory failure shows a significant reduction in the need for extracorporeal membrane oxygenation.³¹ Surfactant may, however, be associated with acute deterioration in the infant's condition and therefore needs to be given with caution.

High frequency ventilation

High frequency ventilation may be helpful in near term infants with respiratory failure. This group of techniques commonly uses high ventilatory frequencies (usually greater than 5 Hz) and tidal volumes that are less than anatomic dead space. Effective ventilation can be achieved because of measurably enhanced mixing, and oxygenation may be improved in some patients, although mean airway pressure changes little. Several reviews of the different high frequency techniques are available.³²

High frequency jet ventilation is probably the most efficient of the techniques in decreasing arterial carbon dioxide pressure, but it may be so efficient that hypocarbia ensues. There are, however, no reliable data to show improved outcome with high frequency techniques in near term infants. Successful normalisation of arterial carbon dioxide pressure can often be achieved with high frequency ventilation in patients in whom conventional ventilation is difficult. However, a randomised controlled trial of high frequency oscillatory ventilation in near term infants with clinically significant lung disease did not show that it reduced the need for extracorporeal membrane oxygenation.³³ A secondary analysis of these data (which should be interpreted cautiously) suggests that some of the infants who did not respond to conventional ventilation were "rescued" with the oscillatory ventilation technique. Recent data in preterm infants showing significant increases in brain injury with jet ventilation³⁴ should stimulate great caution.

Liquid ventilation

Instillation of perfluorocarbon liquid into the lungs rapidly re-expands atelectatic regions, redistributes blood flow, substantially improves compliance by eliminating surface tension forces, and simultaneously supports gas exchange.³⁵ Thus, liquid ventilation may become another method for supporting gas exchange while awaiting recovery from lung disease, at the same time promoting uniform expansion of the lung and possibly administering drugs or surfactant to the lungs.³⁶ Preliminary studies have shown that liquid ventilation is feasible in human neonates, but controls were lacking and survival was not dramatically improved.³⁷ The next phase of investigation of liquid ventilation requires randomised control groups to determine its place in neonatology. Perfluorocarbon treatment may be an effective way of stimulating lung growth, which can occur within a few days,³⁸ and thus may be particularly beneficial in infants with congenital diaphragmatic hernia.

Conclusion

Several new techniques and treatments for supporting near term infants with hypoxia have become available in the past few years. Survival is improved by extracorporeal membrane oxygenation, and inhaled nitric oxide decreases the need for extracorporeal membrane oxygenation without affecting mortality. Exogenous surfactant seems to do the same. The exact roles of high frequency ventilation and liquid ventilation require further investigation.

- Bartlett RH, Roloff DW, Cornell RG, Andrews AF, Dillon PW, Zwischenberger JB. Extracorporeal circulation in neonatal respiratory failure: a prospective randomized study. *Pediatrics* 1985;76:479-87.
- O'Rourke PP, Crone RK, Vacanti JP, Ware JH, Lillehei CW, Parad RB, et al. Extracorporeal membrane oxygenation and conventional medical therapy in neonates with persistent pulmonary hypertension of the newborn: a prospective randomized study. *Pediatrics* 1989;84:957-63.
- Stolar CJH, Snedecor SM, Bartlett RH. Extracorporeal membrane oxygenation and neonatal respiratory failure: experience from the extracorporeal life support organization. *J Pediatr Surg* 1991;26:563-71.
- UK Collaborative ECMO Trial Group. UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation. *Lancet* 1996;348:75-82.
- Delius R, Anderson H, Schumacher R, Shapiro M, Otsu T, Toft K, et al. Venovenous compares favorably with venoarterial access for extracorporeal membrane oxygenation in neonatal respiratory failure. *J Thorac Cardiovasc Surg* 1993;106:329-38.
- Cornish JD, Heiss KF, Clark RH, Strieper MJ, Boecker B, Kesser K. Efficacy of venovenous extracorporeal membrane oxygenation for neonates with respiratory and circulatory compromise. *J Pediatr* 1993;122:105-9.
- Durandy Y, Chevalier JY. Single-cannula venovenous bypass for respiratory membrane lung support. *J Thorac Cardiovasc Surg* 1990;99:404-9.
- Moncada S. The L-arginine: nitric oxide pathway. *Acta Physiol Scand* 1992;145:201-7.
- Etches P, Finer NN, Barrington KJ, Graham AJ, Chan WK. Nitric oxide reverses acute hypoxic pulmonary hypertension in the newborn piglet. *Pediatr Res* 1994;35:15-9.
- Barrington KJ, Finer NN, Peliowski A, Etches PC, Graham AJ, Chan WKY. Inhaled nitric oxide improves oxygenation in a piglet model of meconium aspiration. *Pediatr Pulmonol* 1995;20:27-33.
- North American Inhaled Nitric Oxide (NINOS) Study Group. Inhaled nitric oxide in term and near-term infants with hypoxic respiratory failure. *N Engl J Med* 1997;336:597-604.
- North American Inhaled Nitric Oxide (NINOS) Study Group. Inhaled nitric oxide in near-term infants with congenital diaphragmatic hernia. *Pediatrics* 1997;99:838-45.
- Roberts JD Jr, Fineman J, Morin FC III, Shaul PW, Rimar S, Schreiber MD, et al. Inhaled nitric oxide and persistent pulmonary hypertension of the newborn. *N Engl J Med* 1997;336:605-10.
- Kinsella JP, Truog WE, Walsh WF, Goldberg RN, Bancalari E, Clark RH, et al. Randomized, multicenter trial of inhaled nitric oxide and high frequency ventilation in severe persistent pulmonary hypertension of the newborn. *Pediatr Res* 1996;39:222A.
- Day RW, Lynch JM, White KS, Ward RM. Acute response to inhaled nitric oxide in newborns with respiratory failure and pulmonary hypertension. *Pediatrics* 1996;98:698-705.
- Barefield ES, Karke VA, Phillips JB, Carlo WA. Inhaled nitric oxide in term infants with hypoxemic respiratory failure. *J Pediatr* 1996;129:279-86.
- Wessel D, Agatia I, Thompson J, Kane J, Van Marter L, Stark A, et al. Improved oxygenation in a randomized trial of inhaled nitric oxide for PPHN. *Pediatr Res* 1996;39:252A.
- Barrington KJ, Finer NN. Inhaled nitric oxide for the hypoxic near term neonate. *Cochrane Database of Systematic Reviews* (in press).
- Hogman M, Frostell C, Arnberg H, Sandhagen B, Hedenstierna G. Prolonged bleeding time during nitric oxide inhalation in the rabbit. *Acta Physiol Scand* 1994;151:125-9.
- Rossaint R, Falke KJ, Lopez F, Slama K, Pison U, Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. *N Engl J Med* 1993;328:399-405.
- Zwissler B, Kemming G, Habler O, Kleen M, Merkel M, Haller M, et al. Inhaled prostacyclin (PGI₂) versus inhaled nitric oxide in adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1996;154:1671-7.
- Vane JR, Botting RM. Pharmacodynamic profile of prostacyclin. *Am J Cardiol* 1995;75:3-10A.
- Clark DA, Nieman GF, Thompson JE, Paskanik AM, Rokhar JE, Bredenberg CE. Surfactant displacement by meconium free fatty acids: an alternative explanation for atelectasis in meconium aspiration syndrome. *J Pediatr* 1987;110:765-70.
- Sun B, Curstedt T, Robertson B. Surfactant inhibition in experimental meconium aspiration. *Acta Paediatr* 1993;82:182-9.
- Song GW, Robertson B, Curstedt T, Gan XZ, Huang WX. Surfactant treatment in experimental Escherichia coli pneumonia. *Acta Anaesthesiol Scand* 1996;40:1154-60.
- Nizet V, Gibson RL, Chi EY, Framson PE, Hulse M, Rubens CE. Group B streptococcal beta-hemolysin expression is associated with injury of lung epithelial cells. *Infect Immunol* 1996;64:3818-26.
- Glick PL, Stannard VA, Leach CL, Rossman J, Hosada Y, Morin FC, et al. Pathophysiology of congenital diaphragmatic hernia. II. The fetal lamb CDH model is surfactant deficient. *J Pediatr Surg* 1992;27:382-7.
- Nakamura Y, Yamamoto I, Funatsu Y, Motomura K, Fukuda S. Decreased surfactant level in the lung with oligohydramnios: a morphometric and biochemical study. *J Pediatr* 1988;112:471-4.
- Findlay RD, Taesch HW, Walther FJ. Surfactant replacement therapy for meconium aspiration syndrome. *Pediatrics* 1996;97:48-52.
- Lotze A, Knight GR, Martin GR, Bulas DI, Hull WM, O'Donnell RM, et al. Improved pulmonary outcome after exogenous surfactant therapy for respiratory failure in term infants requiring extracorporeal membrane oxygenation. *J Pediatr* 1993;122:261-8.
- Lotze A, Survanta in Term Infants Study Group. Survanta pre-ecmo trial: multicenter evaluation of survanta in treatment of term infants with severe respiratory failure. *Pediatr Res* 1996;39:226A.
- Froese AB, Bryan AC. High frequency ventilation. *Am Rev Respir Dis* 1987;135:1363-74.
- Clark RH, Yoder BA, Sell MS. Prospective, randomized comparison of high-frequency oscillation and conventional ventilation in candidates for extracorporeal membrane oxygenation. *J Pediatr* 1994;124:447-54.
- Wiswell TE, Graziani LJ, Kornhauser MS, Cullen J, Merton DA, McKee L, et al. High-frequency jet ventilation in the early management of respiratory distress syndrome is associated with a greater risk for adverse outcomes. *Pediatrics* 1996;98:1035-43.
- Fuhrman BP. Perfluorocarbon liquids and respiratory support. *Crit Care Med* 1993;21:951.
- Wolfson MR, Greenspan JS, Shaffer TH. Pulmonary administration of vasoactive substances by perfluorochemical ventilation. *Pediatrics* 1996;97:449-55.
- Leach CL, Greenspan JS, Rubenstein SD, Shaffer TH, Wolfson MR, Jackson JC, et al. Partial liquid ventilation with perflubron in premature infants with severe respiratory distress syndrome. The LiquiVent Study Group. *N Engl J Med* 1996;335:761-7.
- Zhang S, Garbutt V, McBride JT. Strain-induced growth of the immature lung. *J Appl Physiol* 1996;81:1471-6.

Medical school

The Middlesex gnomes

When I went to the Middlesex Hospital in 1948 the courtyard was a delight. Stone flagged it was shaded by tall plane trees, a pleasant oasis in which to walk or sit. In 1949 the site was vandalised, stone flags were replaced by a lawn, and some of the trees were felled. Popular theory held that those in charge were trying to disburse as much of the Middlesex funds as possible before Aneurin Bevan could get his hands on them. Someone said in disgust: "It is getting like a suburban garden, there'll be gnomes next."

John Saxby and I decided to bring this about, and subscriptions to the Gnome Fund were sought. A hilarious telephone conversation followed when John asked to speak to the head of the Gnome Department at Selfridges. We decided that the "One foot gnome complete with copper rod and lead fish" would meet our needs. We had funds for 24 of these. Selfridges had insufficient supplies but rather unwisely revealed the source.

A visit to Cheam confirmed the order, and the gnomes were collected by Francis Rutter with his motorcycle and sidecar. John and I spent a happy weekend painting the gnomes, and they were left to dry in the passage to his flat.

Then with some quick setting cement the gnomes were installed. We sought the most inaccessible ledges and abseiled down to these while the ground crew dealt with the courtyard. We were amazed at how much noise could be made on the roof of a hospital without anyone noticing.

The next morning was fine, and the gnomes sparkled in the sun. Spotting the more obscure ones became a sort of competition. No one, apart from members of the Gnome Fund, had any idea what they meant or why they were there. Numbers dwindled but I was able to show my wife two weatherbeaten survivors in 1957.

D W Smith, retired general practitioner, Rushden, Northamptonshire