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Management of hyaline membrane disease

In 1962, Arshad Warley and Douglas Gairdner wrote 'Management of the condition must at present rest on (1) recognition of the physiological disturbances present in the individual case; and (2) correction of these disturbances, so far as this may be possible, in order that the baby can be given optimal conditions for survival during... a self-limited illness'.[1]

17 years later this statement still summarises perfectly the neonatologist's role in producing neurologically intact survivors from hyaline membrane disease (HMD). The great advances made in recent years in understanding the role and effect of surfactant deficiency in HMD show how both these maxims still apply in the management of the condition. The avoidance of acidaemia, hypothermia, prematurity, and overventilation of the lung, each of which diminishes lung surfactant, is of prime importance in the management of such babies today.

The management of HMD can be considered under three headings. (1) The control, and if possible the normalisation, of the blood-gases. (2) The control, and if possible the normalisation, of the biochemical and physiological abnormalities generally seen in any group of seriously ill patients in intensive care—for example, hypotension, hypothermia, electrolyte imbalances, oliguria, paralytic ileus. (3) The prevention if possible, but otherwise the control of the side effects both of the treatment and the disease—for example, patent ductus arteriosus (PDA) and bronchopulmonary dysplasia.

Control of blood-gases

At the beginning of the 1960s three important studies combined to improve the treatment for infants with HMD. Firstly, Avery and Oppenheimer,[2] in the USA, suggested that the restriction of inspired oxygen concentration to $<40\%$ in an attempt to prevent retrolental fibroplasia (RLF) resulted in a higher mortality from HMD. Cross[3] and Bolton[4] subsequently gave identical data for the UK.

Secondly, Strang and McLeish[5] and Warley and Gairdner[1] showed that the primary defect in oxygenation in HMD was due to right-to-left shunting, and not, among other things, to diffusion difficulties through the hyaline membranes, aptly described as 'eosinophilic red herrings' by Gruenwald.[6]

Thirdly, Ashton[7] showed that it was the oxygen in the blood supplying the retina, rather than the oxygen in contact with the cornea, which caused RLF.

Those paediatricians, in whose view it had always been ridiculous to restrict infants to 40% oxygen, irrespective of cyanosis and progressive vascular collapse, were therefore encouraged to go on administering sufficient oxygen to keep the baby pink and, as arterial blood-gas analysis became available, to keep his Pao_2 in the normal range of 60–90 mmHg (7·98–11·97 kPa).

It was shown that it was possible safely and efficiently to monitor the Pao_2 on blood drawn from an umbilical arterial catheter, without the risk of RLF, and to keep it in this range, while the baby was breathing oxygen concentrations $>40\%$ for prolonged periods of time.[8]

The management of oxygenation in babies with HMD is therefore to increase the inspired oxygen concentration enough to keep the arterial Pao_2 60–90 mmHg. Would that this was all we had to do to keep the Pao_2 normal!

One-third of all babies with HMD so treated in 1968 were still dying. The main reason for death was progressive hypoxaemia and respiratory failure, and the neurological sequelae—such as intraventricular haemorrhage (IVH).[8] Better ways of oxygenating infants were needed and soon were to be provided.

It had long been apparent that breathing was hard work for infants with HMD, and that some way of helping them should be devised. In 1953, Love and Tillery[9] attempted to keep the baby's lungs expanded by attaching a towel clip around the xiphisternum and suspending it from the incubator roof by means of an elastic band. Warley and Gairdner[1] used a variation of this by suspending a weight from a stitch placed under the xiphisternum. Uncontrolled, and uncomfortable, these attempts at what was really continuous positive airways pressure (CPAP) did not achieve clinical acclaim. Yet the report of Gregory and co-workers[10] applying CPAP by endotracheal tube and head box ushered in a new mode of respiratory support for infants with HMD.

Many ways of applying CPAP have been tried but most neonatologists now prefer to use either a closely fitting face mask or nasal prongs, and only apply CPAP via an endotracheal tube when weaning the baby off intermittent positive pressure ventilation (IPPV). Head boxes and bags, and negative pressure chambers have generally been abandoned because they seriously restrict access to the baby and

setting them up involves the excessive handling of the frail, ill infant.

No new technique in the treatment of HMD has so thoroughly been researched and evaluated as CPAP. There can be no doubt that it raises the Pao_2 in infants with HMD, but does this benefit the baby, or does it merely give the physician that inner glow of satisfaction that comes from achieving biochemical normality? Four controlled trials have shown slight benefit, measured in terms of survival, but this was usually restricted to infants weighing $>1 \cdot 5$ kg[11,12,13,14] no doubt due to the fact that in these units the techniques for giving IPPV were so refined that most babies with HMD would have survived regardless of what treatment was given before receiving artificial ventilation.

More germane perhaps is whether CPAP improves the infant's chances in other ways. Theoretically it should; it improves oxygenation, makes respiration more regular,[15] and it lessens surfacant consumption.[16] Durbin and co-workers[13] showed that infants receiving CPAP before IPPV were easier to ventilate. Other studies confirmed that postponing the use of CPAP until HMD was severe, and 70–80% oxygen was required to keep blood-gases normal, resulted in a more prolonged illness that was more likely to progress to the need for IPPV.[17,18,19] However these studies, as was the case with the ones on survival, also showed there was little benefit from giving early CPAP in infants $<1 \cdot 5$ kg, although we now think that these are the very infants who benefit most. Currently we give such infants low pressure CPAP (2–4 cmH_2O) by nasal prong if they show any sign of HMD or if they require increased inspired oxygen concentrations in the first 4–6 hours of life. In larger babies we still keep to the general rule of starting CPAP when $>60\%$ oxygen is required to keep the Pao_2 >60 mmHg.[20]

The use of CPAP can lead to complications, but these are primarily associated with the use of endotracheal tubes or devices with a tight neck seal.[21] When CPAP is applied by means of a mask or prong, the main risk is pneumothorax with an incidence of 20% in some reports. Furthermore one-third of infants requiring CPAP progress to the need for IPPV, and this figure increases to nearly 60% for infants $<1 \cdot 5$ kg.[22] For these reasons CPAP should only be used in neonatal units where high standards of intensive care exist.

In such units there can be no doubt that CPAP has contributed significantly to the survival of infants with HMD, and while it is clearly not a panacea,[23] one can only endorse the view of Chernick[24] 'One or two controlled trials in the use of constant distending pressure in severe HMD, although daring, are welcome; many more would be foolish'.

The medical profession has recently acquired a needless obsession for changing their habits only when convinced by random controlled trials.[25] Fortunately CPAP was generally accepted before the rather dismal results of such trials were published. Few would suggest a need for a trial of IPPV in patients who were apnoeic or merely gasping; to do so would be as ludicrous as a trial of external cardiac massage in cardiac arrest! Yet trials have been done and the cynical reader will not be surprised to find that IPPV only helps particular groups of infants—the smaller ones,[26] the bigger ones,[27] or none![28] In fairness to these studies it should be noted that often ventilators were being used which were less than ideal, and that IPPV was started *before* apnoea and gasping intervened. In North America many infants are still ventilated on the indication of abnormal blood-gas values, but in Britain, influenced by Reynolds,[29] ventilation is rarely started on the basis of poor blood-gases alone.

Much research has gone into how best to ventilate infants with HMD. Reynolds[30] has summarised the current views that most infants on ventilators are optimally oxygenated at rates of 30–40/min with inspiratory:expiratory ratios of about 2:1 and using about 5 cm of positive end expiratory pressure (PEEP). If these guidelines are used, peak inflating pressures exceeding 30 cmH_2O are rarely needed.

The fact that 75–80% of infants $>1 \cdot 0$ kg with HMD who are ventilated because they are apnoeic now survive is surely a vindication (irrespective of random controlled trials) of Donald and Lord's vision in 1953,[31] the same year that Love and Tillery[9] were suspending babies from incubator roofs with elastic bands, that some form of artificial ventilation would enormously improve the chances of survival for these infants.

With CPAP or IPPV it is generally possible to keep most infants with HMD oxygenated. If this fails two other techniques have been advocated. Two reports showed a better survival rate in low birthweight infants with HMD after exchange transfusion with fresh adult blood which increased the P50 of the infant's blood.[32,33] However this has not been confirmed by others,[34] and so the technique has not generally been used. More recently the use of intravenous or intra-arterial tolazoline was shown to improve Pao_2 in infants with severe hypoxaemia from RDS.[35]

Comparatively little attention has been given to the control of CO_2, although as long ago as 1961 it was suggested that this might be a factor in the genesis of IVH.[5] Other than when weaning infants off IPPV it is unusual, in my experience, to see $Paco_2$ values >80 mmHg ($>10 \cdot 64$ kPa), and it has

long been my practice to ignore CO_2 retention if the other blood-gases are satisfactory, particularly in infants with chronic lung disease. However, the neonatal brain blood flow does increase with increased $Paco_2$,[36] and if this is combined with loss, after asphyxia, of autoregulation of cerebral blood flow to changes in blood pressure[37] it is easy to see how the coexistence of hypercapnia, asphyxia, and pronounced changes in blood pressure, which is not uncommon in HMD, could predispose to IVH. In the future perhaps more attention will be paid to keeping the CO_2 under control.

While comparatively little has been written about controlling respiratory acidosis, much has been written about controlling metabolic acidaemia. Four facts need to be remembered when discussing intravenous base therapy in the newborn. (1) With birth asphyxia, the administration of base expedites the onset of breathing and lessens the risk of brain damage.[38,39] (2) The heart works less well when bathed in acid,[40] and the fall in cardiac output thus induced has many secondary effects. (3) Surfactant synthesis turns off at pH $<7{\cdot}25$.[41] (4) Metabolic acidaemia after the first hour of life can be lessened if not stopped by meticulous attention to maintenance of blood volume, oxygenation, and renal function.

Infusing alkali can be harmful. THAM causes apnoea,[42] while bicarbonate causes alarming surges in osmolality and blood volume,[43] and if infused to excess may induce IVH.[44] However rational use of base has not been associated with IVH.[45, 46, 47, 48] The studies implicating bicarbonate treatment in the genesis of IVH have never adequately tackled the possibility that sicker babies, more prone to surges in cerebral blood flow through damaged capillaries, are more likely to have received bicarbonate. Other studies merely confuse the issue—for example by combining IVH with other types of intracranial haemorrhage, such as subdurals which clearly have a different aetiology,[49] or by stating that it is pointless giving bicarbonate in a closed system such as RDS.[50] Clearly it is not.[43]

Routine infusions or bolus injections of base to *all* infants at risk from, or suffering from, mild degrees of acidaemia have been shown to be of no benefit in random controlled trials. Indeed one would hardly expect them to be.[47,51,52,53] There is much information on when, how, and to whom base should not be given. This must be heeded, but it should not detract from the use of bicarbonate in babies with acidaemia >5–10 mmol/l. Since Usher's first study[54] it has been apparent that administration of bicarbonate given at rates <1 mmol/min to carefully selected babies who are acidaemic improves their chances of survival.[55,56]

Control of other physiological abnormalities

Temperature. It has been known since the studies of Blackfan and Yaglou[57] that maintenance of the infant's body temperature was an important component of keeping him alive, and the extensive studies by Hey[58] gave us the basic information needed to keep his core temperature normal. In infants hypoxic with HMD, who are therefore unable to sustain their body temperatures by brown fat metabolism,[59] it is extremely important to regulate the environmental temperature, as surfactant synthesis and function are compromised if the body temperature falls below 35°C.[60,61]

Haematocrit (packed cell volume) and blood pressure. Infants with HMD are more hypotensive and have lower packed cell volumes than unaffected infants, and particularly low values are found in fatal cases.[62,63,64,65] There is no evidence from controlled trials that transfusion to correct anaemia or hypotension, or both, increases the chance of survival, but there is a plethora of clinical experience showing that hypotensive anaemic neonates improve (assessed by improved tissue perfusion and a rising Pao_2) when transfusion is given. Indeed, I always feel embarrassed when discussing the transfusion habits of neonatologists with other physicians as they become slightly patronising when told that we require evidence from controlled trials to justify transfusing a patient who has symptoms of hypovolaemia and a blood pressure half normal.

On the basis of the study of Robinson and co-workers[66] it would seem reasonable to transfuse sick neonates until a systolic blood pressure of about 35 mmHg is attained. Haematocrit values in excess of 40% should also be sustained. This is particularly true for babies being given IPPV plus PEEP for whom the maintenance of an adequate blood volume is essential.[67]

Infection. No one can like the concept of prophylactic antibiotics less than I do. Yet the mortality associated with unrecognised and virtually unrecognisable group B streptococcal sepsis masquerading as HMD immediately after birth is imposing the need to give all dyspnoeic infants a course of benzyl pencillin for at least 48 hours until cultures are known to be negative, unless some clearly noninfectious condition, like pneumothorax or congenital malformation, is responsible for the dyspnoea.[68,69]

Analysis of our data shows that 90% of infants were given antibiotics, either before or shortly after IPPV was begun[22] usually because it was not possible to exclude infection as being the cause for the deterioration which had necessitated the introduction of IPPV.

Feeding. We have I believe, become obsessed with getting food into babies to the point of it becoming harmful. Sick infants have an ileus[70] and it is therefore most unlikely that orally-administered milk will be absorbed. Unpublished analysis of our data showed this to be true. Furthermore feeding causes apnoea and reduces the Pao_2.[71] It also obstructs the nostrils[72] and can introduce germs into the bowel by way of the nasogastric tube.[73] For all these reasons infants with HMD requiring more than 40–50% oxygen or ventilatory assistance should not be fed, nor should they have nasogastric tubes passed for the first 24 to 48 hours. However the very small sick infant will have low caloric reserves that will sustain him for only a few days. For 3 or 4 days he can be given intravenous glucose electrolyte solutions, by which time even if he is on a ventilator having initially been very ill he may show signs of bowel activity—bowel sounds or meconium passage. In such infants, and those recovering from HMD, a nasogastric tube can be passed and milk feeding started, but checks should always be made to ensure that the milk is not pooling in the stomach. In infants who are recovering, oral feeding usually proceeds satisfactorily, but some infants still on IPPV will not tolerate oral feeding, and intravenous feeding should then be begun.

Monitoring. Improved monitoring of the infant during his illness has contributed to the rising survival rate in infants with HMD. Regular blood–gas analysis was established over a decade ago,[8] but within the last few years the use of continuous Pao_2 catheters has stressed the fact that even 3- or 4-hourly sampling of blood–gases gives very poor information about the swings and variations in the infant's oxygenation.[74] Continuous Pao_2 monitoring should now be part of the care for all infants with HMD. Furthermore since access to the arterial tree is required for blood pressure monitoring, pH and Pao_2 analysis, and for biochemical and haematological measurements, I believe that arterial catheterisation remains the procedure of choice for blood–gas monitoring in sick neonates despite the promising results of transcutaneous PO_2 monitoring.[75] Although frequent complications of umbilical artery catheters continue to be reported from the USA this is at complete variance with my own experience both currently and in the past.[76]

The presence of an indwelling arterial catheter enables one to monitor the neonate's oxygen and BP continuously, $Paco_2$, pH, and PCV 3 or 4 times a day, and electrolytes and calcium daily or twice daily as indicated, without breaking that most crucial law of neonatal intensive care—minimal handling. Furthermore the use of continuous Pao_2 catheters has reinforced this law since catheters show the large and potentially damaging falls in Pao_2 which follow even minor interventions.[77] Additionally, ECG and inspired oxygen concentrations should be monitored continuously and some form of apnoea monitoring device must be used, all in ways that give the maximum of information with the least interference to the baby.

The nursing staff by their constant observation and care of the infant, aided by the electronic devices, should be able to detect any minor deterioration in the infant's condition in time for prompt and efficient correction.

Treatment of side effects and associated disorders. With these standards of care the mortality rate from HMD is now about 10%[78] but new problems have appeared. The incidence of PDA[79,80] and necrotising enterocolitis (NEC)[81] in infants with HMD has become a serious matter in the USA although they seem to be less common in the UK. Is there perhaps some factor that links this with their high incidence of umbilical artery occlusions? Certainly, gut hypoperfusion—perhaps induced by an indwelling catheter—is a factor in the aetiology of NEC, and excessive fluid through a catheter may cause PDA.[82]

However out of adversity, some good does come, since the treatment of PDA with prostaglandin synthetase inhibitors[80] must count among the most exciting developments of the decade in neonatal cardiology.

Bronchopulmonary dysplasia (BPD) is a persisting problem on both sides of the Atlantic. Although this was initially attributed to oxygen toxicity[83] this explanation has always seemed naive, as the striking feature identifying cases of BPD was that such babies had received high pressure positive pressure ventilation, and babies have breathed high oxygen concentrations for prolonged periods of time in the past without developing this disease. Reynolds and Taghizadeh[84] showed that in infants with HMD, ventilation designed to lessen the applied pressures reduced the chance of the condition, irrespective of the oxygen concentration, and Stocks and Godfrey[85] showed that persisting abnormalities of respiratory mechanics on such infants are more a function of IPPV than of oxygen therapy. BPD may be minimised by early use of CPAP to lessen the pressures necessary should IPPV subsequently be required.[13]

Conclusion

It is a platitude that prevention is better than cure. Nevertheless it must be said that despite these great improvements in neonatal intensive care it behoves paediatricians to strive to ensure that fewer babies will need to benefit from them.

With better socioeconomic conditions and a higher standard of both general education and antenatal tuition, it is to be hoped that premature labour producing infants at risk from HMD will not only become a rarity but, if it should occur, will be recognised by the mother early enough for newer and more effective tocolytic agents to be administered. These will either prevent delivery or delay it long enough for effective and safe drugs to be used as surfacant inducers, rather than the corticosteroids, heroin, or aminophylline used at present. For the neonate, so lost to all sense of medical decency and decorum to be born without adequate pulmonary surfacant it may soon be possible to give him some.[86]

HMD will become rare but the techniques of management to which Douglas Gairdner and his department in Cambridge contributed so much during the last 20 years, must not be forgotten so that small sick babies with this and other conditions will continue to benefit from high standards of neonatal intensive care.

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