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Neonatal Respiratory Care

Guest Editors: Mei-Jy Jeng, Tsu F. Yeh, Peter A. Dargaville, Thomas H. Shaffer, and Jen-Tien Wung

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Editorial Board

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Editorial

Neonatal Respiratory Care

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Acute respiratory failure caused by different origins continues to be the major etiology of morbidity and mortality in critical neonates. There has been much advancement in neonatal respiratory care, but a few neonates with severe respiratory failure continue to be candidates for extracorporeal membrane oxygenation or survive with chronic lung diseases (CLD). Therefore, searching for ideal respiratory care strategies to reduce the morbidity and mortality rates is crucial for caring critical neonates. The main aim of this special issue was focused on the existing and potential strategies or techniques in neonatal respiratory care. In this special issue, we have invited a few papers that address such issues.

Meconium aspiration syndrome (MAS) is a common cause of severe respiratory failure in term infants. The associations of persistent pulmonary hypertension of newborn (PPHN), pulmonary air leaks, and other morbidities sometimes make the respiratory care a difficult challenge to neonatologists. Three papers address current respiratory care in MAS. In a paper by K. Swarnam et al. they have a detail review on the epidemiology, pathophysiology, and managements in many different views of MAS. In another paper, P. Dargaville focuses on the application of mechanical respiratory supports in MAS, as well as the role of adjunctive respiratory therapies. In a paper, by C. Fischer et al., they demonstrate the epidemiology of MAS in term neonates using a population-based retrospective study for all births from 2000 to 2007 in a French region (Burgundy).

In addition, bronchopulmonary dysplasia (BPD)/chronic lung disease (CLD) continues to be a major cause of neonatal morbidity in spite of significant progress in the treatment of preterm neonates. We have two articles discussing the pharmacologic approaches for prevention and treatment of BPD/CLD. S. Gupta et al. focus on the use of corticosteroids in one paper, and K. Tropea reviews all possible medications and the future potential stem cell therapy in another one.

Furthermore, research papers discussing other important clinical issues in neonatal respiratory care are included. In a paper by S. Rastogi et al., they report their analysis on the factors associated with the successful weaning from nasal continuous positive airway pressure (NCPAP). In a paper by A. Gentili et al., they report their analysis on the

duration of preoperative stabilization in predicting outcome of congenital diaphragmatic hernia. In a paper by K. Hole et al., they report the impact of neonatal resuscitation training in neonatal mortality rates in Malawi, Africa.

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Review Article

Respiratory Support in Meconium Aspiration Syndrome: A Practical Guide

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Meconium aspiration syndrome (MAS) is a complex respiratory disease of the term and near-term neonate. Inhalation of meconium causes airway obstruction, atelectasis, epithelial injury, surfactant inhibition, and pulmonary hypertension, the chief clinical manifestations of which are hypoxaemia and poor lung compliance. Supplemental oxygen is the mainstay of therapy for MAS, with around one-third of infants requiring intubation and mechanical ventilation. For those ventilated, high ventilator pressures, as well as a relatively long inspiratory time and slow ventilator rate, may be necessary to achieve adequate oxygenation. High-frequency ventilation may offer a benefit in infants with refractory hypoxaemia and/or gas trapping. Inhaled nitric oxide is effective in those with pulmonary hypertension, and other adjunctive therapies, including surfactant administration and lung lavage, should be considered in selected cases. With judicious use of available modes of ventilation and adjunctive therapies, infants with even the most severe MAS can usually be supported through the disease, with an acceptably low risk of short- and long-term morbidities.

1. Introduction

Meconium aspiration syndrome (MAS) is complex respiratory disease of the term and near-term neonate that continues to place a considerable burden on neonatal intensive care resources worldwide. The condition has features that make it stand alone amongst neonatal respiratory diseases—the unique combination of airflow obstruction, atelectasis, and lung inflammation, the high risk of coexistent pulmonary hypertension, and the fact of these occurring in a term infant with a relatively mature lung structurally and biochemically. For all these reasons, management of MAS, and in particular the ventilatory management of MAS, has been a difficult challenge for neonatologists down the years. This paper focuses on application of mechanical respiratory support in MAS, as well as the role of adjunctive respiratory therapies. For the purpose of the paper, MAS is defined as respiratory distress occurring soon after delivery in a meconium-stained infant, which is not otherwise explicable and is associated with a typical radiographic appearance [1].

2. Pathophysiology and Effects on Gas Exchange and Lung Compliance

Lung dysfunction in MAS is a variable interplay of several pathophysiological disturbances, chief amongst which are airway obstruction, atelectasis, and pulmonary hypertension. Meconium, the viscid pigmented secretion of the fetal intestinal tract [2], is a noxious substance when inhaled, producing one of the worst forms of aspiration pneumonitis encountered in humans. Meconium has many adverse biophysical properties, including high tenacity (stickiness) [3], very high surface tension (215 mN/m) [3], and potent inhibition of surfactant function [4–6]. It is also directly toxic to the pulmonary epithelium [7], causing a haemorrhagic alveolitis with high concentrations of protein and albumin in the alveolar space [8]. Meconium contains substances that are chemotactic to neutrophils [9] and activate complement [10] and may in addition be vasoactive [11]. These adverse properties of meconium are reflected in the pathophysiological disturbances known to occur in MAS [12].

Once inhaled, migration of meconium down the tracheobronchial tree initially causes obstruction of airways of progressively smaller diameter [13–15]. At least in experimental MAS, there can be a considerable component of "ball-valve" obstruction, with high resistance to airflow in expiration, resulting in gas trapping distal to the obstruction [14]. If global in distribution, high functional residual capacity (FRC) may result, although only in a small proportion of infants with MAS is there measurably high FRC [16, 17], and even then only transiently [17]. For most infants with MAS, the predominant consequence of airway obstruction with meconium is downstream atelectasis [18]. The patchy nature of the airway obstruction results in a juxtaposition of atelectatic and normally aerated lung units, which has been clearly shown histologically [18], and is reflected in the patchy opacification typically noted on chest X-ray in MAS (Figure 1) [19].

After migration to the level of the alveoli, meconium induces a combination of haemorrhagic alveolitis and surfactant inhibition. Meconium is toxic to the alveolar epithelium [7, 20], causing disruption of the alveolocapillary barrier and an exudative oedema not unlike that seen in acute respiratory distress syndrome. The underlying lung interstitium shows inflammatory cell infiltrate [13, 15], and there is a cytokine release in part related to complement activation [10, 21, 22]. Moreover, meconium causes a potent dose-dependent inhibition of surfactant function [4–6] and, along with fibrinogen and haemoglobin in the exudate [23, 24], impairs the capacity of endogenous surfactant to reduce surface tension. Stability of alveoli at end-expiration is thus compromised [25], as is the capacity to clear oedema fluid from the airspaces [26]. The resultant microatelectasis causes variable degrees of ventilation-perfusion mismatch or, worse still, intrapulmonary shunt.

The most prominent and consistent physiological effects resulting from meconium injury are hypoxaemia and decreased lung compliance. Some degree of hypoxaemia is universal in symptomatic MAS, contributed to by many of the above-mentioned noxious effects of meconium. Disturbances of oxygenation in MAS may relate to atelectasis, overdistension, pulmonary hypertension, or a combination of these. A challenging aspect of the management of MAS is to discern which mechanism of hypoxaemia is the predominant one in any given infant at any given time. Particularly where there is prominent airway obstruction or pronounced atelectasis, hypoxaemia may be accompanied by respiratory acidosis with CO_2 retention related to hypoventilation.

Lung or respiratory system compliance is usually significantly impaired in infants requiring ventilation with MAS [17, 22, 27–30]. Experimental studies have indicated that decreased compliance may be related to hyperinflation secondary to "ball-valve" airway obstruction [14], and the combination of poor compliance and high FRC has been demonstrated in some cases of MAS [17]. For most infants with MAS, in whom FRC is normal or low [17], poor compliance relates to global or regional atelectasis. Application of mechanical ventilation further complicates the picture, potentially leading to overdistension of relatively unaffected lung regions which, due to their relatively long time constant, may empty incompletely during the ventilator expiratory cycle, especially at fast ventilator rates [31]. Respiratory resistance has also been noted to be increased in some studies, but variations in the technique of measurement make interpretation of these results difficult.

MAS is frequently accompanied by persistent pulmonary hypertension of the newborn (PPHN) [32], with many factors contributing to its development, including low pO_2 and pH, coexistent intrauterine asphyxia, and possibly vasoactive substances in the meconium itself [33].

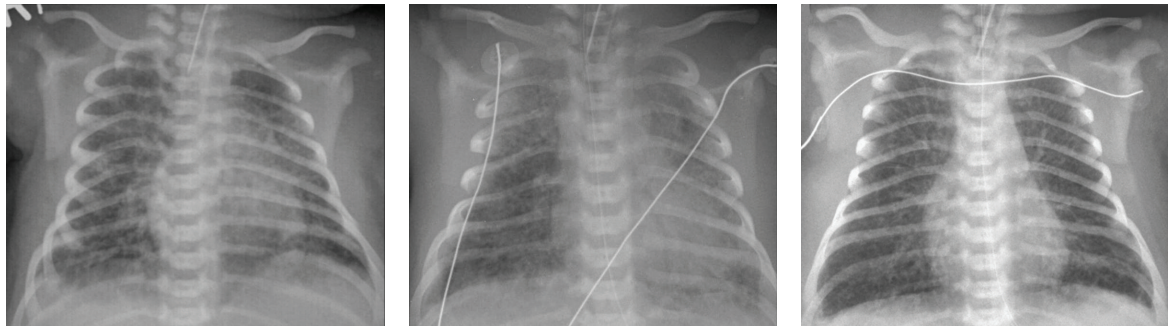
3. Stepwise Approach to Respiratory Support

3.1. Oxygen Therapy. Supplemental oxygen administration is the mainstay of treatment for MAS and in many less severe cases is the only therapy required [34]. Some ventilated infants with MAS receive high inspired oxygen concentration for long periods, with few apparent adverse effects. Therapeutic considerations in cases of persistently high oxygen requirement are outlined in Table 1.

As with the preterm infant, moment-by-moment adjustment of oxygen concentration (or flow) in infants with MAS is guided oxygen saturation measured by pulse oximetry (SpO_2). Given the high incidence of right-to-left ductal shunting related to pulmonary hypertension, a pre-ductal SpO_2 is preferable, with the target range for SpO_2 being higher than that for the preterm infant, usually between 94 and 98%. In ventilated infants, oxygen therapy can also be monitored by blood gas sampling from an intra-arterial line, preferably in a preductal position in the right radial artery. Suggested target pO_2 range is 60–100 mm Hg (preductal). Where there is considerable PPHN, titration of FiO_2 using postductal pO_2 values is not advisable.

3.2. Continuous Positive Airway Pressure. Of all infants requiring mechanical respiratory support because of MAS, approximately 10–20% are treated with continuous positive airway pressure (CPAP) alone [34–36]. Additionally, up to one-quarter of infants requiring intubation with MAS receive CPAP before and/or after their period of ventilation [36]. CPAP for such infants can be effectively delivered by binasal prongs or a single nasal prong, typically with a CPAP pressure of 5–8 cm H_2O. Tolerance of the CPAP device may be limited given the relative maturity of infants with MAS, and on occasions the associated discomfort will exacerbate pulmonary hypertension to the point where intubation becomes necessary.

3.3. Intubation. Approximately one-third of all infants with a diagnosis of MAS require intubation and mechanical ventilation [33, 37]. Indications for intubation of infants with MAS include (a) high oxygen requirement ($FiO_2 > 0.8$), (b) respiratory acidosis, with arterial pH persistently less than 7.25, (c) pulmonary hypertension, and (d) circulatory compromise, with poor systemic blood pressure and perfusion [38]. Except in emergency circumstances, intubation of infants with MAS should be performed with premedication. Significant endotracheal tube leak is a major barrier to



(a) (b) (c)

Figure 1: Chest X-ray appearances in ventilated infants with MAS. (a) Typical appearance of MAS showing "fluffy" opacification widespread throughout the lung fields. (b) Marked atelectasis in an infant with profound hypoxaemia. (c) Hyperinflation and gas trapping, with a narrow cardiac waist, flattened diaphragms, and intercostal bulging of the lung.

Table 1: Approach to hypoxaemia in MAS.

If there is marked global or regional atelectasis, consider:
(i) Increasing PEEP to improve end-expiratory lung volume
(ii) Increasing PIP to recruit atelectatic lung units
(iii) Increasing inspiratory time to facilitate the recruiting effect of PIP
(iv) Use of HFOV with sufficient distending pressure to recruit atelectatic lung units
(v) Use of HFJV with sufficient PEEP to maintain FRC and conventional breath PIP to recruit atelectatic lung units
(vi) Exogenous surfactant
(vii) Lung lavage
If there is obvious gas trapping, consider:
(i) Decreasing PEEP (but may lose recruitment of areas prone to atelectasis)
(ii) Decreasing inspiratory time and increasing expiratory time
(iii) Use of HFJV with low PEEP, low frequency (240–360 bpm), and minimal CMV breaths
(iv) Use of HFOV with relatively low P_{AW} and low frequency (5-6 Hz)
If there is pulmonary hypertension, consider:
(i) Correction of potentiating factors—hypoglycaemia, hypocalcaemia, hypomagnesaemia, polycythaemia, hypothermia, pain
(ii) Bolstering systemic blood pressure to reduce right to left ductal shunt—volume expansion, pressor agents
(iii) Improving right ventricular function—inotrope infusion
(iv) Selective pulmonary vasodilators—inhaled nitric oxide

effective ventilation in infants with MAS, and in most cases a size 3.5 mm internal diameter endotracheal tube will be required. Once intubated, tolerance of the endotracheal tube will almost certainly require ongoing sedation with infusions of an opiate (e.g., morphine or fentanyl) [39], possibly supplemented with a benzodiazepine. Additionally, continuation of muscle relaxant drugs is often helpful during the stabilisation period after intubation, particularly in infants with coexistent pulmonary hypertension.

3.4. Conventional Mechanical Ventilation. Despite more than four decades of mechanical ventilation for infants with MAS, the ventilatory management of the condition remains largely in the realm of "art" rather than "science", with very few clinical trials upon which to base definitive recommendations. Physiological principles and published experience do, however, allow some guiding principles to be put forward for conventional ventilation strategy in MAS.

3.4.1. Choosing a Mode of Ventilation. Ventilation mode and the value of patient-triggering have been incompletely studied in MAS. Two randomised trials of patient-triggered ventilation have included infants with MAS. One of these found no advantage of synchronised intermittent mandatory ventilation (SIMV) over IMV in 15 infants with MAS [40]. Another study found, in a group of 93 infants >2 kg birth weight (including an unspecified number with MAS), that use of SIMV was associated with a shorter duration of ventilation compared with IMV [41]. Despite the relative paucity of evidence in favour, it seems logical to use a synchronized mode of ventilation in any spontaneously breathing ventilated infant with MAS. Trigger sensitivity should be set somewhat higher than that for a preterm infant and should take into account the possibility of autocycling if there is a tube leak [42]. There have been no clinical trials in patients with MAS comparing SIMV and synchronised intermittent positive pressure ventilation (SIPPV), also known as assist control. Given the propensity for gas trapping in MAS, there is some concern that using SIPPV may lead to high levels of inadvertent positive end-expiratory pressure (PEEP) with resultant hyperinflation. For this reason SIMV may be the most appropriate mode of ventilation in MAS.

3.4.2. Selection of Positive End-Expiratory Pressure. For any newborn respiratory disease, but particularly MAS, application of PEEP must balance the competing interests of overcoming atelectasis whilst avoiding overdistension. Early observations of the effect of PEEP suggested the greatest benefit with PEEP settings between 4 and 7 cm H_2O,

with higher PEEP settings (8–14 cm H_2O) giving minimal oxygenation benefit [43]. No more recent clinical studies exist to guide PEEP selection in MAS. Physiological principles dictate that if atelectasis predominates (Figure 1(b)), increasing PEEP (up to a maximum of 10 cm H_2O) should improve oxygenation, whereas for regional or global hyperinflation (Figure 1(c)) a lower PEEP (3-4 cm H_2O) may be effective (Table 1) [38]. For infants with severe atelectasis, PEEP settings above 10 cm H_2O are likely to increase the risk of pneumothorax [44], and modes of high frequency ventilation are to be preferred if available.

3.4.3. Selection of Inspiratory Time. As with PEEP, setting inspiratory time in MAS must take into account the balance between atelectasis and overdistension. Term infants have generally longer time constants than their preterm counterparts [45] and thus require a longer inspiratory time (around 0.5 sec) to allow near-full equilibration of lung volume change in response to the applied peak pressure. Even longer inspiratory times may be useful for lung recruitment during inspiration if atelectasis is prominent.

3.4.4. Selection of Peak Inspiratory Pressure (or Tidal Volume). Given the reduced compliance, the peak inspiratory pressure (PIP) required to generate sufficient tidal volume in MAS is often high (30 cm H_2O or more). Such pressures may well contribute to a secondary ventilator-induced lung injury in ventilated infants with MAS. Suggested target tidal volume is 5-6 mL/kg. If using a "volume guarantee" mode, the peak pressure limit should be set at or near 30 cm H_2O to allow the ventilator to scale up the PIP when needed to reach the tidal volume target. If PIP is persistently higher than 30 cm H_2O, high frequency ventilation should be considered, if available.

3.4.5. Selection of Ventilator Rate. Especially if there is gas-trapping and expiratory airflow limitation, optimal conventional ventilation in MAS requires the use of a relatively low ventilator rate (<50) and hence longer expiratory time. This will help to avoid inadvertent PEEP. The resultant minute ventilation must be sufficient to produce adequate CO_2 clearance. An acceptable arterial pCO_2 range is 40–60 mm Hg and pH 7.3-7.4, which is achievable in most infants even when there is significant parenchymal disease combined with PPHN [46]. Hyperventilation-induced alkalosis, which anecdotally appeared to reduce the need for extracorporeal membrane oxygenation (ECMO) in infants with PPHN [47], is no longer practiced, in part due to the risk of sensorineural hearing loss [48].

3.5. High-Frequency Oscillatory Ventilation. Despite the dearth of clinical trial, evidence suggesting a benefit, high frequency oscillatory ventilation (HFOV) has become an important means of providing respiratory support for infants with severe MAS failing conventional ventilation. Published series from large neonatal databases suggest that 20–30% of all infants requiring intubation and ventilation with MAS are treated with high-frequency ventilation [34, 36, 49], with most of these receiving HFOV rather than high-frequency jet ventilation (HFJV). Indications for transitioning to HFOV include ongoing hypoxaemia and/or high FiO_2, and, less commonly, respiratory acidosis. In infants with significant atelectasis, adequate lung recruitment may require the application of a mean airway pressure (P_{AW}) considerably higher than that on conventional ventilation (up to 25 cm H_2O in some cases), with a stepwise recruitment manoeuvre likely to be the most effective [50]. Once oxygenation has improved, P_{AW} should then be reduced; most infants with MAS requiring HFOV can be stabilised using a P_{AW} around 16–20 cm H_2O, with gradual weaning in the days thereafter [51]. Infants with prominent gas trapping may tolerate the recruitment process poorly, with reductions in oxygenation and systemic blood pressure and the potential for exacerbation of pulmonary hypertension. Recruitment manoeuvres of some form can still be advantageous in this group, with the benefit becoming apparent when the P_{AW} is reduced.

Choice of oscillatory frequency is critically important in MAS, with experimental studies and clinical experience indicating that frequency should not be higher than 10 Hz and preferably should be set at 8 or even 6 Hz. In experimental models of MAS, high oscillatory frequency (15 Hz) is associated with worsening of gas trapping [52]. HFOV can also lend a clinical advantage in infants with significant coexisting PPHN, as the response to inhaled nitric oxide (iNO) is better when delivered on HFOV compared to conventional ventilation [53]. Early reports suggested that up to half of infants with MAS treated with HFOV did not respond adequately and went on to receive ECMO [54, 55]. More recent experience would suggest that only around 5% of infants treated with HFOV and iNO fail to respond and undergo transition to ECMO [36].

3.6. High-Frequency Jet Ventilation. The combination of atelectasis and gas trapping that can occur in MAS may be better managed with HFJV than HFOV (Table 1), with the former technique offering the possibility of ventilation at a lower P_{AW} [56]. A number of laboratory investigations have shown HFJV, either alone or in combination with surfactant therapy, to be beneficial in animal models of MAS [18, 56, 57]. Clinical studies including infants with MAS appear to confirm the benefit of HFJV compared with conventional ventilation, both in terms of improvement in oxygenation, and avoidance of ECMO [58, 59]. Whilst there have been no direct comparisons with HFOV in a clinical setting, we have noted that some infants with intractable hypoxaemia and/or respiratory acidosis do show improvements after transition from HFOV to HFJV using a low-frequency (240–360 bpm) and a low conventional ventilator rate [60].

4. Adjunctive Respiratory Therapies

4.1. Bolus Surfactant Therapy. The pathophysiology of MAS includes inhibition of surfactant in the airspaces, both by meconium and exuded plasma proteins [4–6, 23]. Preliminary reports of the use of exogenous surfactant given as bolus therapy to ventilated infants with MAS were promising,

although it was identified that around 40% of cases did not respond [61]. Four randomised controlled trials of bolus surfactant therapy have been conducted [62–65], which when analysed together show a benefit in terms of reduction in need for ECMO but not duration of ventilation or other pulmonary outcomes [66]. In the developed world, bolus surfactant therapy is currently used in 30–50% of ventilated infants with MAS [34, 36]. Bolus surfactant therapy should be used judiciously in MAS, choosing infants with severe disease, and treating early and, if necessary, repeatedly [12].

4.2. Lavage Therapy. Lung lavage using dilute surfactant is an emerging treatment for MAS that offers the potential of interrupting the pathogenesis of the disease by removal of meconium from the airspaces [12]. Laboratory studies and preliminary clinical evaluations have indicated that lavage therapy may improve oxygenation and shorten duration of ventilation in MAS [67–69]. A recent randomised controlled trial of large-volume lavage using dilute surfactant in infants with severe MAS noted no effect on duration of respiratory support or other pulmonary outcomes but did find a higher rate of ECMO-free survival in the treated group [70]. Further clinical trials will be necessary to more precisely define the effect on survival.

4.3. Corticosteroid Therapy. Steroid therapy has been investigated in MAS for more than 3 decades, with a number of small clinical trials being conducted, none of which have given a definitive result. One recent trial suggested that dexamethasone therapy could dampen the inflammatory response in MAS [71]. In the absence of further trials, steroid therapy cannot be recommended as routine therapy in MAS.

4.4. Inhaled Nitric Oxide. Large randomised controlled trials have demonstrated the effectiveness of iNO in term infants with pulmonary hypertension, with a reduction in need for ECMO and in the composite outcome of death or requirement for ECMO [72]. Each trial included a large subgroup with MAS; overall more than 640 infants with MAS have been enrolled in iNO trials, although few have reported the outcome for MAS separately. The potential value of delivering iNO during HFOV has been highlighted in one trial, in which the proportion of nonresponders was lowest when the two therapies were combined [53]. Currently around 20–30% of all ventilated infants with MAS receive iNO [34, 36], and around 40–60% show a sustained response [46, 53].

The approach to an infant with MAS and coexistent PPHN should initially focus on optimising the ventilatory management and in particular overcoming atelectasis whilst avoiding hyperinflation, both of which are associated with an increase in pulmonary vascular resistance. The severity of PPHN should be assessed clinically and by echocardiogram if available. If moderate-severe PPHN persists after appropriate ventilatory manoeuvres and the pO_2 remains at less than 80–100 mm Hg in FiO_2 1.0 [53, 73], iNO should commence at a dose of 10–20 ppm. Higher doses do not appear to result in better oxygenation [74].

4.5. Extracorporeal Membrane Oxygenation. Infants with severe MAS have been treated with ECMO since 1976, and MAS has been the leading diagnosis amongst neonates referred for this therapy [75]. ECMO is now available to infants with MAS in selected centres in 33 countries worldwide [76], albeit at a high cost (at least 2.5 times the daily cost of standard intensive care) [77]. With the advent of newer therapies, the number of infants with MAS treated with ECMO has decreased [78], but survival with ECMO treatment for MAS has remained high (around 95%) [75]. The usual indication for commencing ECMO is intractable hypoxaemia despite optimisation of the patient's condition with available therapies (including high-frequency ventilation and iNO) and bolus surfactant therapy). Degree of hypoxaemia in this setting has generally been quantified using oxygenation index (OI), where $OI = P_{AW} \times FiO_2 \times 100/PaO_2$. An OI persistently above 40 despite aggressive standard management has been, and remains, an indication for treatment with ECMO where available [79]. Followup of newborn infants treated with ECMO because of parenchymal lung disease (excluding diaphragmatic hernia) suggests a low rate of severe disability at one year (1.7% in the UK ECMO trial) [80], with the risk of any disability being 17% [80].

4.6. Liquid Ventilation. To the author's knowledge, there is as yet no report of clinical use of perfluorocarbon in MAS. Both total liquid ventilation with perfluorocarbon and perfluorocarbon-assisted gas exchange have been investigated in animal models of MAS [81–83]. Both techniques have shown short-term advantages over conventional ventilatory management, with better oxygenation and lung compliance [81, 83]. Total liquid ventilation appears to be the most lung protective, resulting in much reduced meconium-associated histological damage compared with conventional ventilation or PAGE [81]. The complications of perfluorocarbon instillation noted in human subjects, including pneumothorax, impaired carbon dioxide clearance, and delayed excretion, may be significant barriers to the clinical use of liquid ventilation in ventilated infants with MAS.

Perfluorocarbon has also been considered as a possible vehicle for lung lavage in MAS, especially given the favourable biophysical properties including high oxygen carrying capacity and low surface tension. Despite these potential advantages, use of neither pure [84] nor emulsified [69] perfluorocarbon as a lavage fluid has shown any major advantage over dilute surfactant. Even when followed by perfluorocarbon-assisted gas exchange, the benefits of perfluorocarbon lavage appear minimal [83]. This may be due to the relatively high density of perfluorocarbon and/or the relative immiscibility of meconium with perfluorochemicals.

5. Outcome of Ventilation in MAS

5.1. Duration of Ventilation and Oxygen Therapy. Considering all intubated infants with MAS, median duration of ventilation is 3 days (mean 4.8 days) [36]. Infants with more severe disease, requiring at least one of high-frequency

ventilation, iNO or bolus surfactant, are ventilated for a median of 5 days [36]. Median duration of oxygen therapy and length of hospital stay currently stand at 7 and 17 days, respectively [36].

5.2. Mortality. Refinements in intensive care and respiratory support have contributed to a significant decrease in mortality related to MAS, with population-based studies now suggesting a mortality of 1-2 per 100,000 live births [36, 85, 86]. The case-fatality rate in ventilated infants with MAS varies widely in published series (0–37%) [37] and is influenced by availability of alternative means of ventilation, adjunctive therapies including nitric oxide, and ECMO. Approximately one-quarter to one-third of all deaths in ventilated infants with a diagnosis of MAS are directly attributable to the pulmonary disease, with the remainder in large part caused by hypoxic-ischaemic encephalopathy [34, 36, 86].

5.3. Short-Term Morbidities. Pneumothorax occurs in around 10% of all ventilated infants with MAS [36, 87], and the presence of this complication potentiates lung atelectasis and PPHN and increases the risk of mortality [36, 88]. Other air leak syndromes, including pneumomediastinum and pulmonary interstitial emphysema, are seen occasionally. Pulmonary haemorrhage (or, more correctly, haemorrhagic pulmonary oedema) occurs in a small proportion of infants with MAS and can occasionally cause severe destabilisation and hypoxaemia [89].

5.4. Long-Term Morbidities. Respiratory compromise after hospital discharge is common in infants who were ventilated with MAS. Up to half of infants will be symptomatic with wheezing and coughing in the first year of life [90]. Older children may exhibit evidence of airway obstruction, hyperinflation, and airway hyperreactivity, but appear to have normal aerobic capacity [91]. Neurological sequelae following MAS are well recognized [37], and a diagnosis of MAS in the neonatal period confers a considerable risk of cerebral palsy (5–10%) [92, 93] and global developmental delay (15%) [92].

6. Conclusion

With judicious use of available modes of ventilation and adjunctive therapies, infants with even the most severe MAS can usually be supported through the disease, with an acceptable burden of short-and long-term morbidity.

Conflict of Interests

No conflict of interests is declared.

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Clinical Study

Is the Time Necessary to Obtain Preoperative Stabilization a Predictive Index of Outcome in Neonatal Congenital Diaphragmatic Hernia?

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Background. The study aims to verify if the time of preoperative stabilization (≤24 or >24 hours) could be predictive for the severity of clinical condition among patients affected by congenital diaphragmatic hernia. *Methods*. 55 of the 73 patients enrolled in the study achieved presurgical stabilization and underwent surgical correction. Respiratory and hemodynamic indexes, postnatal scores, the need for advanced respiratory support, the length of HFOV, tracheal intubation, PICU, and hospital stay were compared between patients reaching stabilization in ≤24 or >24 hours. *Results*. Both groups had a 100% survival rate. Neonates stabilized in ≤24 hours are more regular in the postoperative period and had an easier intensive care path; those taking >24 hours showed more complications and their care path was longer and more complex. *Conclusions*. The length of preoperative stabilization does not affect mortality, but is a valid parameter to identify difficulties in survivors' clinical pathway.

1. Introduction

Congenital diaphragmatic hernia (CDH) is a rare but serious disorder of the newborn, that occurs in 1/2000 to 1/5000 live births a year, and still has an elevated mortality (20–50%). The prognosis of these patients, even if it has become better than in the past, still remains unsatisfactory despite the recent acknowledgements about diagnosis, physiopathology, and treatment [1, 2].

The degree of lung hypoplasia, the persistence of pulmonary hypertension, and the rate of antenatal termination are the main factors that influence the prognosis [3]. Furthermore, in the presence of serious cardiac defects, the outcome of infants with CDH is extremely poor [4]. Associations with complex syndromes and chromosomal defects also worsen the prognosis [5].

The use of advanced respiratory support techniques, such as extracorporeal membrane oxygenation (ECMO), high-frequency oscillatory ventilation (HFOV), inhaled nitric oxide (iNO), and surfactant administration, which have been introduced over the last 10–15 years for the treatment of CDH patients, seems to have been able to improve their clinical patterns.

Important progress has also been made through the international collaboration provided by groups and institutions such as the CDH Study Group, the American Academy, and the CDH EURO Consortium [6–8]. Their, studies, involving collections of data and common reports, standardized postnatal management and followup shared by many centers, have surely done much to promote the awareness and treatment of this pathology, thereby improving diagnostic and therapeutic approaches.

In addition, many studies underline that CDH outcome might be influenced by the choice of undergoing surgical repair when a state of clinical stability has been achieved [5, 9–11].

A determining aspect in the whole clinical pathway of CDH patients, both during pregnancy and after birth, is

the analysis of factors that could be predictive of outcome, with regards to both mortality and treatment complexity.

The literature proposes many studies on CDH disease severity involving the application of both prognosis-related factors measured singularly during pregnancy or at birth, or some predictive outcome models and scores [6, 12–16].

This study intends to assess whether the time needed for CDH patients to obtain preoperative stabilization (≤24 hours or >24 hours) could be predictive for the complexity of the whole clinical path of such patients.

2. Materials and Methods

Between January 2000 and December 2010, 77 consecutive neonates affected by CDH were treated at the Paediatric Intensive Care Unit (PICU) of our hospital. Table 1 summarizes the main characteristics of the enrolled patients.

After obtaining written, informed parental consent, all patients were treated with the same protocol:

(i) continuous intravenous analgosedation with midazolam (2-3 mcg/kg/min) and fentanyl (2–4 mcg/kg/h);

(ii) early HFOV used as the first choice and configured with mean airway pressure (MAP) between 9.5 and 14 cm H_2O, delta P between 26 and 45 cm H_2O, 10 Hz respiratory frequency, inspiratory time 33%, and FiO_2 adjusted to maintain the paO_2 between 80 and 100 mmHg;

(iii) fluid intake between 60 and 90 mL/kg/day;

(iv) volemic expansion with fresh frozen plasma (20–30 mL/kg/die);

(v) cardiac inotropic support with dobutamine and/or dopamine (5–10 mcg/kg/min);

(vi) inhaled nitric oxide started at a dose of 20 ppm in the case of pulmonary hypertension;

(vii) porcine-derived surfactant (70–100 mg/kg) administered if hypoxia occurred (paO_2 < 60 mmHg with FiO_2 > 0.8) without pulmonary hypertension associated with right-to-left shunt.

Both invasive and noninvasive cardiocirculatory monitoring (heart rate, pre- and postductal systolic, diastolic, mean blood pressure, and central venous pressure) were performed. Patients also underwent pre- and postductal arterial oxygen-saturation (SpO_2), central body temperature, blood lactate values, and urine output. Echocardiography was made to check for cardiovascular anomalies, right and left ventricle performance, pulmonary artery pressure, and ductal shunting. Chest X-ray completed the respiratory evaluation, focusing on lung recruitment and mediastinum alignment.

CDH treatment strategy included medical stabilization before surgery, which was achieved when the patients reached and maintained for at least five hours the regularization of the following parameters, irrespective of the day of evaluation:

Table 1: Perinatal data of 77 patients affected by CDH.

Patient characteristics	
Male/female	49 (63.6%)/28 (36.4%)
Birth weight (gr)	2930 ± 485 (range 4300-1800)
Gestational age at delivery (wk)	37 ± 2 (range 42–32)
Term/preterm delivery	40 (52%)/37 (48%)
Left/right side	67 (87%)/10 (13%)
Inborn/outborn	71 (92.2%)/6 (7.8%)
Prenatal diagnosis	68 (88.3%)
Associated anomalies	18 (23.4%)
Associated congenital heart diseases	4 (5.2%)

(i) five respiratory and blood-gas-derived indexes: the oxygenation index (OI) < 10, the alveolar-arterial O_2 gradient ($A\text{-}aDO_2$) < 250 mmHg, the arterial-alveolar O_2 tension ratio (a/AO_2) > 0.5, $paCO_2$ < 55 mmHg and arterial pH > 7.35 during HFOV with $FiO_2 \leq 0.50$ and map ≤13;

(ii) four hemodynamic and metabolic parameters: mean arterial pressure (MAP) within normal level for gestational age, absence of right-to-left ductal shunt, urine output ≥1.5 mL/kg/h, and lactate blood level below 3 mmol/L.

Only 73 patients were enrolled in the study, since 4 neonates with severe associated congenital heart diseases, characterized by intracardiac shunts, were excluded. Patent ductus arteriosus and patent foramen ovale were not classed as cardiovascular malformations.

The surgical approach was abdominal. A subcostal transverse muscle cutting incision was made on the site of the hernia, whose contents were gently reduced in the abdomen. Most diaphragmatic defects were repaired by direct sutures of the edges of the defect. A prosthetic material (1 mm Gore-Tex) was used for wide defects (>3.5 cm).

The neonates were weaned back to conventional ventilation only postoperatively, when respiratory and blood-gas-derived indexes became and remained within their normal range and $FiO_2 \leq 0.40$, Delta $P \leq 36$ cm H_2O, and map ≤12.

In order to fulfil the aim of the study, the CDH patients who were considered stable and underwent surgical repair were divided into two groups (patients who became stable in less than or at 24 hours versus those whose stabilization required more than 24 hours). The survival rate, the trend of respiratory and blood-gas-derived and hemodynamic indexes of medical stabilization (OI, $A\text{-}aDO_2$, a/AO_2, arterial pH and $paCO_2$, MAP, absence of right-to-left ductal shunt, urine output, and lactate level) at three times (PICU admission, before surgery, and after surgery), the need for advanced respiratory support (iNO and surfactant) and other intensive care data (days of HFOV, days of tracheal intubation, length of stay in PICU and in hospital) were compared between the two groups. The difference between the two groups was also analysed using various neonatal scores: Apgar score at 1 and 5 minutes, CDHSG (CDH-Study-Group) equation at birth, SNAP II (Score for Neonatal

Table 2: Trend of respiratory, blood-gas-derived, hemodynamic, and metabolic indexes at the three considered times (PICU admission, before surgery, after surgery) in the 55 patients stabilized and submitted to surgery, divided into two groups according to the duration of preoperative stabilization stage (≤24 hours or >24 hours).

	PICU admission		Before surgery		After surgery		P
Indexes	≤24 h	>24 h	≤24 h	>24 h	≤24 h	>24 h	
OI	12.4 ± 12.7	15.0 ± 10.5	5.6 ± 7.6	6.0 ± 4.9	4.5 ± 6.6	9.5 ± 8.9	ns
A-aDO_2 (mmHg)	354 ± 158	369 ± 167	169 ± 122	207 ± 105	151 ± 110	220 ± 118	0.039
a/AO_2	0.28 ± 0.20	0.23 ± 0.18	0.54 ± 0.19	0.45 ± 0.25	0.56 ± 0.19	0.41 ± 0.23	0.047
paCO_2 (mmHg)	46.7 ± 4.7	61.4 ± 6.3	37.4 ± 1.4	39.5 ± 1.9	36.6 ± 1.7	45.0 ± 2.3	0.015
pH	7.29 ± 0.19	7.25 ± 0.21	7.41 ± 0.12	7.44 ± 0.09	7.43 ± 0.12	7.42 ± 0.15	ns
PAM (mmHg)	41.5 ± 8.1	39.7 ± 8.7	42.3 ± 9.3	38.9 ± 7.7	42.1 ± 6.8	37.4 ± 6.7	ns
Urine output (mL/h)	1.65 ± 0.84	1.19 ± 0.78	2.14 ± 0.77	1.83 ± 0.65	1.96 ± 0.91	1.52 ± 0.76	0.048
Lactate (mmol/L)	1.8 ± 0.4	2.1 ± 0.7	1.2 ± 0.5	1.5 ± 0.4	1.4 ± 0.6	1.9 ± 0.9	ns
No R-L shunt	26/33 (79%)	4/22 (19%)	33/33 (100%)	22/22 (100%)	33/33 (100%)	20/22 (90%)	ns

Acute Physiology), SNAPPE II (SNAP Perinatal Extension II), PRISM III (Pediatric Risk of Mortality III), and WHSRpf (Wilford-Hall/Santa-Rosa formula).

The Apgar score at 1 and 5 minutes is determined by evaluating the newborn baby on five simple criteria on a scale from zero to two, then summing up the five values thus obtained. The resulting Apgar score ranges from zero to 10. The five criteria (Appearance, Pulse, Grimace, Activity, and Respiration) are used as a mnemonic aid. Scores 3 and below are generally regarded as critically low, 4 to 6 fairly low, and 7 to 10 generally normal [17].

The CDHSG score is generated from 2 descriptive data points (birth weight and 5-minute Apgar) within the first 5 minutes of life; the obtained score value divides the neonates into 3 groups with a predicted low risk (survival rate > 66%), intermediate risk (survival rate 34–66%), and high risk (survival rate < 33%) [6].

SNAP II measures the severity of illness in infants by utilizing physiological data collected during the first 12 hrs of care. It consists of six items, including the lowest mean blood pressure, lowest temperature, lowest pH, lowest PaO_2/FiO_2 ratio, urine output, and the presence of multiple seizures. SNAP II has also been modified for use as a mortality prediction model (SNAPPE II) by including birth weight, small-for-gestational age, and low Apgar score. Some dedicated tables relate the obtained score with predicted mortality [12, 18].

PRISM III is comprised of 17 clinical variables subdivided into 26 ranges that include physiological and laboratory measurements that are weighted on a logistic scale. PRISM III is an adequate indicator of mortality probability for heterogeneous patient groups in pediatric intensive care. Patients with PRISM scores of >10 are considered at high risk [19, 20].

WHSRpf formula uses blood gas values measured during the first 24 hours of life to calculate the equation: highest paO_2— highest $paCO_2$, with a cutoff value of zero or greater expected to predict survival [13].

Statistical analysis was performed using univariate logistic regression, Friedman test, Fisher exact test, and Mann-Whitney test; the null hypothesis was rejected when $P < 0.05$.

3. Results

A total of 77 consecutive patients were affected by CDH, with an overall survival of 72.7%. The 4 patients with associated congenital heart diseases excluded from the study presented 1 left ventricle hypoplasia, 2 Fallot tetralogies, and 1 interventricular defect.

Of the 73 patients included in the study, 55 (75.4%) reached presurgical stabilization, confirmed by the achievement of the five preestablished values of respiratory and blood-gas-derived indexes and of the four hemodynamic and metabolic parameters previously specified. 18 patients (24.6%) died before surgery, having never achieved clinical stabilization: 11 of these died within the first 24 hours, 5 within 48 hours, and 2 within 72 hours after birth. The cause of death was the suprasystemic pulmonary hypertension with right-to-left ductal shunt and the right cardiac failure associated with acute respiratory failure unresponsive to treatment.

The 55 patients underwent a surgical correction after a stabilization interval of 43.9 ± 38.7 hours (range 22–168); 33 reached clinical stability in less than or at 24 hours after PICU admission (group I), while 22 required a stabilization time of more than 24 hours (group II), with a mean of 77.8 ± 45.9 hours after PICU admission (range 30–168).

In both groups submitted to surgery the survival rate was 100%. No deaths occurred among the patients without associated congenital heart diseases, but they were considered stable and submitted to surgical repair of CDH. Survival was defined as survival to discharge from the hospital.

Table 2 shows that the respiratory and blood-gas-derived and hemodynamic index values are consistently outside the normal range at PICU admission, confirming the cardiorespiratory pattern severity for these patients. The values were normalized before surgery and after surgery in both groups. However, more stable and physiological levels can be noted in the group of patients reaching preoperative stabilization within 24 hours, in comparison to those who were stabilized after more than 24 hours. Among the considered indexes, A-aDO_2, a/AO_2, paCO_2, and urine output showed a statistical significance. Another noteworthy difference between the two

Table 3: Comparison of severity scores in the 55 patients stabilized and submitted to surgery, divided into two groups according to the duration of preoperative stabilization stage (≤24 hours or >24 hours).

Scores	≤24 h	>24 h	*P*
APGAR 1 min	6.3 ± 1.6	5.1 ± 1.9	0.025
APGAR 5 min	7.7 ± 1.2	6.8 ± 1.7	0.033
CDHsg	75 ± 16	67 ± 13	ns
PRISM	13.22 ± 4.81	16.81 ± 8.32	ns
SNAP II	13.03 ± 9.99	19.74 ± 17.90	ns
SNAPPE II	18 ± 14	32 ± 23	0.016
WHSRpf	156 ± 109	144 ± 111	ns

Table 4: Comparison of advanced respiratory therapies and the timing of intensive care and hospital treatment in patients stabilized and submitted to surgery, divided into two groups according to the duration of preoperative stabilization stage (≤24 hours or > 24 hours).

Parameter	≤24 h	>24 h	*P*
iNO treatment	7/33 (21.2%)	18/22 (81.8%)	0.018
Surfactant treatment	9/31 (29.0%)	11/19 (57.8%)	0.041
HFO (days)	5.2 ± 4.6	7.4 ± 5.2	0.032
IRT (days)	21.6 ± 18.2	26.3 ± 17.5	0.228
PICU (days)	23.1 ± 13.7	34.1 ± 19.6	0.017
Hospital (days)	35.3 ± 12.1	43.1 ± 14.5	0.029

groups is that in group I the index values after surgery improved or remained the same as before surgery, whereas in group II the neonates tended to show a slight worsening of these indexes immediately after surgery.

In addition, all the predictive outcome models and scores analysed (Table 3) show worse values, farther outside normal ranges, and in the neonates who stabilized after 24 hours. In particular, we underline the fact that the Apgar score at 1 and 5 minutes and SNAPPE II show statistically significant differences between the two groups.

Finally, the advanced respiratory support application rates (iNO and surfactant) and certain intensive care timing indexes (days of HFO, days of tracheal intubation, and length of stay in PICU and in hospital) were significantly higher in the survivors requiring more than 24 hours for preoperative stabilization (Table 4).

4. Discussion

CDH shows a broad spectrum of clinical variability, thus making it very difficult to formulate a correct prognosis. At birth, in fact, one may find moderately compromised clinical conditions, or, conversely, dramatic cardiorespiratory patterns, that require immediate and highly invasive treatments that are not always successful [21, 22].

CDH is characterized by a variable degree of pulmonary hypoplasia associated with a decrease in the number of bronchial generations, alveoli, and pulmonary vessels and an increase in the muscularity of the pulmonary vascular bed. The hypoplastic lung has a small alveolar capillary membrane for gas exchange, which may be further decreased by the surfactant system dysfunction. Pulmonary capillary blood flow is decreased because of the small cross-sectional area of the pulmonary vascular bed, and flow may be further decreased by abnormal pulmonary vasoconstriction, which can be increased by a vicious circle sustained by hypoxia, hypercapnia, acidosis, and hypothermia [3, 23–25].

The clinical use of advanced respiratory assistance strategies, such as ECMO, HFOV, and iNO administration as a selective pulmonary vasodilator and surfactant administration, has surely improved CDH prognosis, but global mortality remains high, between 20 and 50%, in reported case series from all over the world [1, 2, 21, 22].

The goal to understand the best timing, according to the clinical pattern, to perform CDH surgical correction has reached a good level of consensus in the literature [5, 6, 8–11, 26–29]. The study by Nakayama et al. , which demonstrated the utility of preoperative stabilization in improving respiratory compliance of CDH patients, had a fundamental role in proposing delayed surgical treatment [30]. A further step towards understanding the concept of CDH preoperative timing was achieved with subsequent studies that demonstrated how the improvement in CDH survival was due to cardiorespiratory stability more than the time between birth and surgery [31, 32]. In fact, the aim to achieve preoperative stabilization, irrespective of the time taken, is a priority in CDH treatment, since it is well known that surgical correction performed in a compensated condition can give the patient more survival chances. This is possible only with an improvement in respiratory failure (better ventilation of hypoplastic lung and recruitment of contralateral lung), and with the interruption of the right-to-left ductal shunt characteristic of suprasystemic pulmonary hypertension during the phase of CDH decompensation, in order to ameliorate hemodynamic performance [33–35].

CDH has a number of characteristic anatomical and physiopathological features, due to the neonatal age and to the specific pulmonary malformation. It could therefore be hypothesized that the use of some specific indexes and neonatal scores may be predictive of the severity and the clinical path of such pathology.

The application of predictive outcome indexes becomes particularly important in the early postnatal period, during which estimating the severity of the disease can promptly indicate the most appropriate therapies to undertake. On the basis of the achievement of specific values of five respiratory and blood-gas-derived indexes (OI, A-aDO_2, a/AO_2, $paCO_2$, and arterial pH) and four hemodynamic and metabolic parameters (MAP, right-to-left ductal shunt absence, urine output, and lactate blood level), it was possible to determine the most opportune moment to submit the patients to surgery. The respiratory and hemodynamic indexes in question are often a commonly applied tool to assess the degree of cardiorespiratory failure in neonatal and paediatric age, but they can also well express the compensation conditions in patients affected by pathologies such as CDH [8, 36–38]. The literature shows how the failure to achieve validated indexes

for the assessment of cardiorespiratory compensation in neonates affected by CDH may inhibit surgical repair [8, 29, 36, 39]. In our study, in fact, 18 patients died without having ever achieved a phase of compensation and without being submitted to surgery. On the other hand, all 55 patients who achieved preoperative stabilization, irrespective of the time taken (≤24 hours or >24 hours), presented a 100% postoperative survival, thus confirming the validity of the treatment undertaken and of the parameters chosen to define preoperative stabilization and the moment for surgical repair.

Some of the scores adopted, such as the CDHSG and WHSRpf, are specific for the assessment of outcome in CDH [6, 13]. SNAP II and SNAPPE II, which were initially validated outcome predictors in the non-CDH neonatal population, have also been reported as predictors of mortality in infants with CDH [12]. The Apgar score at 1 and 5 minutes and PRISM III are more generic scores, in that they assess respectively the newborn baby at birth and heterogeneous pediatric patient groups in NICU/PICU [17, 20]. Our data shows that the greatest part of the considered postnatal scores are reliable and concordant in CDH outcome: the values of these scores are in fact prognostically associated with a favourable outcome, in line with the complete survival registered in patients defined stable and submitted to surgery.

The present study also shows that the different duration of preoperative stabilization stage (≤24 hours or >24 hours) is indispensable for assessing the best moment in each patient to undergo surgical repair; it does not affect mortality given that all the patients considered stable survived, but can be considered a reliable index to assess the complexity and clinical severity of CDH in survivors.

The preoperative stabilization time divides the neonate survivors into two groups. The first is characterised by a normalization of the parameters within 24 hours, immediately followed by surgery. These patients show a correspondence between favourable outcome factors, good stability of the respiratory, blood-gas-derived and hemodynamic values, and a short clinical path. They belong to the category of patients that the literature on CDH reports as the most regular and the most compensated [5, 9, 11, 40]. The second group is characterized by the need for stabilization times longer than 24 hours and consequently a more delayed surgical repair. The latter patients are characterized both by more altered predictive outcome scores and by the fact that all respiratory, blood-gas-derived, hemodynamic, and metabolic indexes of clinical stabilization tend to worsen (within normal range) in the early postoperative period compared to the immediate preoperative stage and to the patients who became stabilized in the first 24 hours. In addition, these patients needed more frequent surfactant and iNO administration, and longer HFOV, tracheal intubation times, and prolonged length of PICU and hospital stay, if compared with patients needing less than 24 hours to achieve stability. Some of them probably belong to the category of patients who in the past were destined for an unfavourable prognosis but who now appear to have benefitted from the introduction of new treatment modalities and advanced respiratory support techniques [2, 41, 42].

5. Conclusions

Recent reports continue to confirm that CDH is a serious and severe neonatal pathology still afflicted by high mortality, that can present variable clinical pictures at birth and that requires immediate and graded steps of treatment depending on the respiratory distress and the persistence of pulmonary hypertension [8, 28, 31]. The possibility to have valid and precise indexes of reference in terms of outcome can help obtain a prompt and correct therapeutic framework.

Our study confirms the need to submit CDH patients to surgery only if they have achieved conditions of stability clearly grounded on precise parameters. Thanks to the achievement of such criteria, surgery can be performed with greater confidence and with the knowledge that a high survival rate can be expected. The study underlines that the length of preoperative stabilization does not affect mortality, but has proved a valid index in pinpointing difficulties throughout the patient's whole pathway. When the time needed for neonates to achieve stabilization is short (≤24 hours), they remain more stable in the postoperative period and have an easier and more linear intensive care path; when the time of preoperative stabilization is longer (>24 hours), the neonates are more complicated, need more intensive therapy, and have a longer and more complex care path, even after surgery.

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Review Article

Current Pharmacologic Approaches for Prevention and Treatment of Bronchopulmonary Dysplasia

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Bronchopulmonary dysplasia (BPD) is a major complication of preterm birth and has serious adverse long-term health consequences. The etiology of BPD is complex, multifactorial, and incompletely understood. Contributing factors include ventilator-induced lung injury, exposure to toxic oxygen levels, and infection. Several preventive and therapeutic strategies have been developed with variable success. These include lung protective ventilator strategies and pharmacological and nutritional interventions. These strategies target different components and stages of the disease process and they are commonly used in combination. The purpose of this review is to discuss the evidence for current pharmacological interventions and identify future therapeutic modalities that appear promising in the prevention and management of BPD. Continued improved understanding of BPD pathogenesis leads to opportunities for newer preventive approaches. These will need to be evaluated in the setting of current clinical practice in order to assess their efficacy.

1. Introduction

Bronchopulmonary dysplasia (BPD) remains a major complication of prematurity resulting in significant mortality and morbidity despite advances in perinatal care and decline in mortality rates among very low birth weight (VLBW) infants [1]. Increased survival among VLBW infants contributes to the overall increase in the incidence of BPD and currently infants with birth weights <1250 grams account for 97% of cases of BPD [2]. The long-term health consequences of BPD include respiratory disease that can persist into adulthood and increased susceptibility to respiratory infections, asthma, pulmonary hypertension, repeated hospitalizations, neurodevelopmental impairment, and also increased mortality [3]. The etiology of BPD is multifactorial and includes exposure to mechanical ventilation, oxygen toxicity, infection, and inflammation that contribute to arrested alveolar development and associated abnormal vascular growth and damage to the distal airways of the highly vulnerable premature lung [4]. Multiple pharmacological and nonpharmacological approaches have been proposed for the prevention or treatment of preterm lung injury and BPD. While antenatal steroids, protective ventilation strategies, targeted oxygen saturation goals, caffeine therapy, vitamin A therapy, and optimization of nutrition have helped to modestly improve BPD outcomes, most current therapies are supportive [4, 5]. Many therapies remain controversial due to unacceptable side effects and others continue to need further study including randomized controlled trial testing and long-term outcome follow-up analysis.

In this review, we present the current and potential future pharmacologic approaches for the prevention and management of BPD based on published meta-analyses, randomized controlled trials, systematic reviews, individual clinical studies, and emerging work from animal models of disease. A comprehensive list of the drugs discussed in the prevention and management of BPD is shown in Table 1.

2. Caffeine

Caffeine is a methylxanthine commonly used in the treatment of apnea of prematurity, a common complication of

Table 1: Pharmacological interventions for prevention and management of BPD.

Class of drugs	Presumed mechanism	Main clinical responses	Major side effects	Recommended use in BPD
Caffeine	Apnea of prematurity Unknown	Reduction in days of positive pressure ventilation, reduction in BPD, lower incidence of neurodevelopmental impairment	Transient decrease in weight gain	Recommended for treatment of apnea of prematurity and prevention of BPD
Diuretics *(loop, thiazides)*	Pulmonary Edema	Decreased pulmonary edema	Electrolyte imbalance, osteopenia, ototoxicity	*Loop:* use sparingly in early evolving BPD *Thiazides:* Consider for judicious chronic use
Bronchodilators *(albuterol, ipratropium)*	Bronchospasm	Bronchodilation	Tachycardia, arrhythmias	Limit use in infants with bronchospasm and acute clinical response
Steroids *(early, moderately early, late, inhaled)*	Inflammation	Improved oxygenation, earlier extubation	Short term: hyperglycemia, hypertension, GI perforation Long term: increased risk for cerebral palsy	Last resort therapy for rapidly deteriorating pulmonary status
Mast cell stabilizer *(cromolyn)*	Inflammation	No clinical benefit	None reported	Not for routine use
Vitamin A	Impaired lung development	Small reduction in incidence of BPD	None reported	Recommended in infants <1000 grams
Inositol	Impaired lung growth	Decreased incidence of BPD	None reported	Not for routine use
Antioxidants *(SOD, NAC, Vitamin E, vitamin C)*	Oxidant injury	Delayed benefit from SOD	None reported	Not for routine use
Inhaled NO	Inflammation Oxidant stress Unknown	Possibly beneficial in reducing BPD but optimal timing, dose and duration unknown	IVH in infants <1000 g with early rescue use	Not for routine or rescue use

Modified from Baveja and Christou [10].

prematurity occurring in at least 85 percent of infants who are born at less than 34-week gestation [6, 7]. Methylxanthines have been shown to reduce the frequency of apnea of prematurity and need for mechanical ventilation during the first seven days of therapy [8]. A recent large randomized controlled trial followed primary outcome of long-term neurodevelopment and secondary short-term outcomes of rates of BPD in infants with birthweights from 500 to 1250 grams [8]. Infants in the caffeine group were found to have an incidence of BPD of 36% compared to 47% of infants in the placebo group [8]. Patients in the caffeine group had reduced weight gain, but this was found to be temporary. Long-term follow-up at 18 to 22 months showed that infants assigned to the caffeine group had a lower incidence of neurodevelopmental impairment including lower rates of cerebral palsy and lower rates of cognitive delay [9]. The potential mechanism of the effect of caffeine on decreased incidence of BPD remains unknown. The number of days on positive pressure ventilation was decreased by one week in the infants assigned to the caffeine group which could account for potential reduction in ventilator-induced lung injury in the caffeine group [8, 9]. When interpreting this secondary outcome of caffeine leading to a decreased rate of BPD, it is important to take into consideration that the randomization protocol effectively excluded infants who needed mechanical ventilation for greater than 10 days, in other words infants at a presumably higher risk for BPD. In conclusion, the evidence supports the use of caffeine in treatment of apnea of prematurity with findings of secondary benefits including reduction in BPD rates and improved neurodevelopmental outcomes.

3. Diuretics

Diuretics are a common class of drugs used in the management of BPD. Interstitial alveolar edema appears to be a prominent feature of BPD and excessive interstitial edema can lead to decreased lung compliance. Iatrogenic increase in fluid administration, capillary leak from inflammation due to infection or from ventilator-induced lung injury, and volume overload due to left to right shunting through a patent ductus arteriosus are some of the factors that contribute to pulmonary edema [11–13]. Diuretics potentially benefit by increasing reabsorption of fluid from the lung.

(a) Loop Diuretics. Loop diuretics act by blocking the luminal Na-K-2Cl transporter in the thick ascending limb of the loop of Henle. Loop diuretics compete for the chloride site on this transporter and diminish reabsorption. Furosemide is the most widely administered loop diuretic in neonates; yet its use remains controversial. A Cochrane meta-analysis has reviewed several small trials that studied the risks and benefits of systemic furosemide on preterm infants with BPD [14]. Minimal effect was observed with enteral furosemide in preterm infants <3 weeks of age [14]. Chronic administration of furosemide for a week improved short-term outcomes of pulmonary compliance, oxygen requirement, and minute ventilation in preterm infants >3 weeks of age with BPD [15–17]. However, no existing trials have addressed long-term outcomes including effect on duration of oxygen requirement, weaning off mechanical ventilation, duration of hospital stay, incidence of BPD, and mortality [14].

Administration of aerosolized furosemide has also been explored in an effort to minimize systemic side effects in preterm infants with evolving BPD. A Cochrane meta-analysis reviewed 8 trials with aerosolized furosemide and noted that a single-aerosolized dose of furosemide may transiently improve pulmonary mechanics in preterm infants >3 weeks of age [18]. There was no significant pulmonary improvement with chronic administration of aerosolized furosemide. None of these studies examined delivery of the drug to the distal airways or serum levels. Furthermore, the studies had inadequate assessment of clinical outcomes such as duration of mechanical ventilation, oxygen requirement, length of stay, incidence of BPD, mortality, and complications of treatment.

In summary, the data on the use of furosemide is limited. Potential risks of loop diuretic therapy such as electrolyte imbalance, ototoxicity, nephrocalcinosis, and osteopenia along with inconclusive data on long-term primary and secondary outcomes warrant future trials to justify the chronic use of furosemide in current clinical practice. Current evidence does not support use of loop diuretics for prevention of BPD and use of furosemide sparingly to acutely treat pulmonary edema is currently the preferred practice.

(b) Thiazides. Thiazides effect the early portion of the distal tubule and bind directly to the chloride site of the electroneutral sodium chloride channel. The risk of electrolyte abnormalities is far less with thiazide diuretics compared to loop diuretics due to the small amount of sodium absorption occurring in the distal tubule. A Cochrane meta-analysis examined six studies on the use of thiazides in preterm infants and found that chronic use of thiazides improves lung mechanics and decreases the need for supplemental furosemide boluses [19]. In a randomized double-blind placebo-controlled trial thiazide and spironolactone were given to 43 nonintubated BPD patients until they no longer required oxygen supplementation [20]. The study showed decreased oxygen requirement and improved lung function in the treatment group compared to placebo but failed to show any improvement in the survival rate, duration of oxygen requirement, or length of hospital stay. In intubated patients, a lower oxygen requirement and better lung compliance and decreased administration of furosemide boluses in the treatment group compared to placebo were found in one study, but with no change in airway resistance [21]. Administration of thiazides did not decrease the length of hospital stay, need for ventilator support, or other long-term outcomes. Addition of potassium-sparing diuretics such as spironolactone which act exclusively on the Na−K/H exchange mechanisms in the late distal tubule and cortical collecting duct did not alter the compliance or oxygen requirement compared to thiazides alone and had no effect on need for electrolyte supplementations [22].

Further studies on the role of chronic diuretics in the treatment of BPD may be warranted in the current practice era of antenatal steroids and surfactant therapy in order to provide definitive evidence of their clinical usefulness. No clear evidence is present for use of thiazide diuretics for the prevention or management of BPD. Meanwhile thiazides are the diuretics of choice in ventilator-dependent infants for specific case-based administration and care should be taken to avoid electrolyte abnormalities with appropriate supplementation.

4. Bronchodilators

BPD causes increased airway resistance due to smooth muscle hypertrophy and hyperreactivity [3]. Bronchodilators are a common medication used to relieve bronchospasm in asthmatic patients and have been studied in BPD patients. Studies have shown that bronchospasm contributes to elevated pulmonary resistance in preterm infants and bronchodilators improve dynamic compliance by lowering pulmonary resistance [23–26]. Bronchodilators have been broadly categorized into adrenergic and anticholinergic agents. Their effect is transient and both have been shown to acutely reduce pulmonary resistance and increase compliance in BPD patients. Variability in individual responsiveness to β-agonists may be genetically determined [27–29]. In the Cochrane database only one trial addressed the use of bronchodilators for the prevention of BPD and measured long-term outcomes [30]. The study enrolled 173 infants <31 weeks of gestational age, who needed ventilatory support at the 10th postnatal day. They were randomized to four groups and received either placebo, placebo with salbutamol or beclomethasone, or both beclomethasone and salbutamol for 28 days. No significant effects of the treatment on incidence or severity of BPD, duration of ventilator support, or oxygen therapy were observed.

The two most widely used bronchodilators are albuterol and ipratropium [23, 31]. Potential side effects of β sympathomimetic agents include tachycardia, hypokalemia, arrhythmias, and hyperglycemia. Inhaled anticholinergic agents, in addition, decrease gastrointestinal motility and dry and thicken respiratory secretions. Ipratropium has traditionally been used along with albuterol to provide synergism. No trials have yet investigated if a combination therapy of a beta agonist and anticholinergic result in improved outcomes in BPD compared to albuterol alone. Future trials are required

to study various modes of delivery of the different adrenergic and anticholinergic drugs alone or in combination.

Due to a low number of trials and potential side effects, current evidence supports that bronchodilator therapy should be limited to infants with evidence of bronchospasm and continued only if there is a clinical response to therapy. Even in these cases, there is no evidence that the long-term outcome is altered.

5. Steroids

Inflammation is a main contributor to the pathogenesis of BPD. Since corticosteroids are potent anti-inflammatory agents, many trials have examined the use of steroids in BPD. Systemic steroid administration reduces the inflammatory response, produces a rapid improvement in pulmonary function with better gas exchange, and facilitates weaning from mechanical ventilation. In addition to the anti-inflammatory effects, steroids also enhance surfactant production, decrease airway edema, stabilize capillary leakage, augment β adrenergic activity, and decrease overall lung fibrosis [32–34]. Both systemic and inhaled corticosteroids have been studied extensively in preterm neonates for prevention and treatment of BPD. The steroid trials may be categorized according to the time of administration. Early administration is defined as less than eight days after birth. A Cochrane meta-analysis reviewed that twenty-eight randomized controlled trials evaluated effects of early treatment of dexamethasone on the incidence of BPD [35, 36]. Steroids facilitated extubation and decreased the incidence of BPD. However, adverse effects such as hyperglycemia, gastrointestinal perforation, hypertension, infection, steroid-induced cardiomyopathy, and long-term neurodevelopmental effects including cerebral palsy complicated the treatment. Moderately early administration of dexamethasone (between 7 to 14 days) led to similar decrease in the incidence of BPD and facilitated extubation [37]. Nine trials studied late administration of dexamethasone usually after 3 weeks [38]. These studies showed transient improvement including increased success rates of extubation and reduction of the need for later steroid and home oxygen therapy compared to the controls. Both moderately early and late treatments were complicated by short- and long-term side effects. The most worrisome long-term effect increased risk for poor neurological outcome including cerebral palsy. As a result, the European Association of Perinatal Medicine, the American Academy of Pediatrics, and the Canadian Pediatric Society have advised against routine use of systemic dexamethasone for the prevention or treatment of BPD. One study has examined the use of low-dose dexamethasone (0.89 mg/kg over 10 days) in preterm infants who were ventilator dependent after 1 week of age [39]. The study showed decreased ventilator requirement, improved oxygenation, and greater percentage of successful extubation in the treatment group compared to placebo. Although the study showed no short-term side effects such as hypertension or intestinal perforation, it enrolled relatively "older" premature infants (mean gestational age 28-29 weeks) and no long-term outcomes were included.

In summary, the evidence of long-term neurodevelopmental harm with administration of steroids is clear with early (<8 day) administration of dexamethasone [36]. With later administration (>7 days), the data trended towards increased cerebral palsy along with a trend towards decreased mortality [37, 38].

Given these findings of increased likelihood of poor neurological outcome, current evidence is clearly against the early use of dexamethasone in the first week of life. Later use of dexamethasone should be undertaken with caution and reserved for patients with BPD in whom weaning from high ventilator settings and oxygen support is unsuccessful or their respiratory status is rapidly deteriorating.

Recent arguments have questioned the use of dexamethasone in the steroid trials and the possible role of other steroids. Betamethasone, a stereoisomer of dexamethasone, may have a differential role in preterm infants. Some have reported concern of possible direct neuronal injury and neurological side effects from the preservatives such as sulfites present in dexamathasone and potential further study of postnatal betamethasone may be warranted [40, 41]. Hydrocortisone prophylaxis for early adrenal insufficiency to prevent BPD was examined [42]. In this study, preterm infants weighing less than 1 kg and mechanically ventilated were randomized to receive placebo or hydrocortisone, 1 mg/kg/day for 12 days and then 0.5 mg/kg/day for 3 days. The study showed no significant differences in the survival rates between the two groups. However, among infants exposed to chorioamnionitis, the ones treated with hydrocortisone had significantly lower mortality and improved survival without BPD. There was no suppression of adrenal function or short-term growth but a higher rate of gastrointestinal perforation was seen in the hydrocortisone-treated group receiving indomethacin compared to the placebo group. Additional trials may be warranted in order to determine the role of low-dose hydrocortisone therapy in the prevention of BPD especially in preterm infants born to mothers with chorioamnionitis.

Inhaled steroids have also been evaluated in an effort to optimize the benefits of corticosteroids and minimize unacceptable systemic side effects. Inhaled steroids have been tried early (<2 weeks of age) to prevent BPD and later to treat established BPD [43, 44]. None of the trials demonstrated significant change on the BPD rate at 28 days or 36 weeks postmenstrual age. Multiple trials examined the effectiveness of inhaled steroids administered to ventilator dependent preterm infants after two weeks of life [45–48]. These approaches offered no advantage of aerosolized corticosteroids over systemic therapy. Aerosolized steroids did not have any significant effect on the mortality or incidence of BPD, duration of ventilatory support, or oxygen therapy. Major concerns with inhaled corticosteroids included the type of steroids, their dosages, and uncertainty regarding drug delivery. Studies have suggested that delivery of aerosolized particles is limited by the size of the particles, presence or absence of endotracheal tube to facilitate delivery, differences in delivery device (i.e., MDI versus spacer), and use of nebulizers. There is some evidence that inhaled steroids are absorbed systemically and thus

carry risks similar to systemic steroids. At the time of this review, a multicenter randomized controlled clinical trial is underway in Europe (NEuroSIS) aiming to examine whether early administration of inhaled steroids in preterm infants reduces the risk of BPD and includes short-term and long-term outcomes which may answer questions regarding both efficacy as well as safety. Due to their multiple mechanisms of action, steroids continue to offer promise in the prevention and management of BPD; however, the appropriate dose, timing, and size of the glucocorticoid molecule need to be further studied in order to maximize benefit and minimize risks. These studies must include long-term pulmonary and neurodevelopmental follow-up in order to determine whether the intervention is safe and effective.

6. Mast Cell Stabilizer

Cromolyn, a mast cell stabilizer, is the first nonsteroidal anti-inflammatory drug used in asthmatic patients. It targets both sensitized and nonsensitized mast cells and prevents degranulation and release of histamine. Mast cell stabilizers have been shown to decrease neutrophil migration and activation thus minimizing inflammation [49]. Two trials studied the possible role of cromolyn in prevention and treatment of evolving BPD [49, 50]. Though the sample sizes were small, both studies showed no improvement in mortality, days on mechanical ventilation, or incidence of BPD. Cytokine levels were lower in the lung lavage fluid in the treatment group compared to the placebo [49]. These studies, similar to other aerosolized drug studies, did not assess drug delivery, thus failing to provide evidence for effective drug deposition. Current evidence does not support the use of cromolyn for the prevention or treatment of BPD but further studies may be warranted.

7. Vitamin A

Vitamin A is a retinoid essential for the normal lung growth and important in regulation of lung epithelial cell repair. It is known that preterm infants have low levels of Vitamin A at birth with low levels associated with an increased risk of chronic lung disease [51]. A Cochrane meta-analysis reviewed eight studies on the efficacy of Vitamin A supplementation in prevention of BPD. In extremely low birth weight infants, supplementation was found to decrease rates of BPD [52]. In the largest trial in the meta-analysis, infants less than 1000 grams who received vitamin A supplementation had an 8% decrease in rate of death or BPD compared to the placebo group [53]. While this meta-analysis includes eight studies, the study by Tyson et al. is clearly the largest and greatly influences the results. Enteral application of high-dose vitamin A was examined in one study that did not show any long-term positive effect [54]. The current evidence solely supports the intramuscular delivery of high-dose vitamin A to ELBW infants [53]. Neurodevelopmental outcomes at 18 to 22 months were not different in the two experimental groups; interestingly there was also no difference in respiratory outcome at 18 to 22 months [55]. Evidence supports the use of high-dose intramuscular vitamin A supplementation for the prevention of BPD in premature infants <1000 grams although there are no long-term benefits in pulmonary or neurodevelopmental outcome.

8. Inositol

Inositol is a phospholipid that enhances the synthesis and secretion of surfactant phospholipids thereby improving pulmonary function. A randomized controlled trial by Hallman et al. demonstrated lower oxygen and airway pressure requirements with the use of intravenous inositol; however very few patients received surfactant in this trial [56]. Within the group receiving surfactant, there was no reduction in BPD after inositol administration in this study. A Cochrane meta-analysis that included all infants who received inositol treatment showed a significant reduction in death or BPD compared to untreated controls [57]. No further studies to confirm these findings have been reported; it is possible that the positive results previously found would no longer be present in the surfactant era or that inositol administration may benefit a subpopulation of infants. Inositol is not currently recommended for prevention of BPD but further trials may be warranted in the surfactant era to confirm these preliminary findings and to study the long-term effects.

9. Antioxidants

(a) Superoxide Dismutase (SOD). Free radicals have been implicated in the pathogenesis of BPD. Premature infants are susceptible to oxidant injury since they are relatively deficient in antioxidant enzymes while being exposed to toxic oxygen levels [58]. Preliminary animal and human studies have provided evidence for a protective action of antioxidants such as SOD in hyperoxia-induced acute and chronic lung injury [59–61]. A randomized controlled trial studied if recombinant CuZnSOD would decrease the incidence of BPD in ventilated and surfactant-treated preterm infants [62]. This trial enrolled 302 patients and showed that CuZn-SOD can be given safely and is well tolerated intratracheally but found no difference in the primary outcome of BPD at 28 days of life or 36 weeks postmenstrual age. The striking result was a significant decrease in several indicators of lung disease in the treatment group over the first year of life including reduction in need for asthma medications, fewer emergency department visits, and fewer hospitalizations suggesting a delayed beneficial response at one year of age in infants <27 weeks gestation. The mechanism underlying this SOD-mediated delayed benefit is unclear but presumably involves the disruption of the pathogenic reactive oxygen species. It appears that the role of SOD in the management of BPD may warrant further study. The long-term effect of SOD in other neonatal morbidities and the effects of dosage, mode of delivery, frequency, and type of preparation of SOD need to be addressed in future trials.

(b) N Acetyl-Cysteine (NAC). Glutathione is an endogenous scavenger of free radicals, which is relatively deficient in

premature infants with decreasing gestational age [63]. Ahola et al. proposed use of NAC, a precursor of glutathione, to ameliorate cellular injury from free radicals [64]. Intravenous NAC was administered for the first six postnatal days in a multicenter double blind placebo-controlled trial. In a group of 391 infants weighing under 1000 g, no significant differences were found in incidence or severity of BPD between the NAC and placebo groups [64]. A follow-up study showed no significant difference in the lung function between the two groups [65]. Long-term follow-up of these infants will be required to determine potential delayed benefits.

(c) Tocopherol (Vitamin E) and Ascorbic Acid (Vitamin C). Both Vitamin E and C could serve as scavengers of reactive oxygen species produced during high oxygen exposure and prevent lipid peroxidation. Randomized controlled trials have shown no evidence that vitamin E supplementation alone or in combination with vitamin C offers protection against BPD [66, 67].Although the mechanism is well established, limited success has been achieved using antioxidants and therefore their routine use is not recommended at present. Potential limiting factors include radical formation restricted to subcellular compartments, timing, dose, and delivery of the drug, or perhaps a need for multiple agents blocking different pathways of reactive oxygen species. Alternatively, as the SOD trial has shown, lack of acute benefit does not preclude delayed beneficial effects on pulmonary outcome. This underscores the importance of including long-term outcomes in the design of randomized trials of pharmacologic interventions for BPD.

10. Inhaled Nitric Oxide (iNO)

iNO is a selective pulmonary vasodilator that decreases pulmonary vascular resistance without affecting systemic vascular tone [68]. The rationale for the use of iNO in the prevention of BPD stems from animal and human studies supporting an anti-inflammatory role for NO and beneficial effects in lung structure and gas exchange [69–73]. Several large clinical trials with different study designs yielded variable results [74–79]. These studies included iNO given as prophylaxis to prevent BPD, as rescue therapy for severe acute respiratory failure, and as treatment for severe BPD in a variable patient population. One of the larger trials by Ballard et al. enrolled intubated infants during the second postnatal week and used a higher starting dose of iNO and demonstrated a modest reduction in BPD in the treatment group, but no difference in death [74]. While a modest reduction in composite outcome of death or BPD was found in a systematic review, there was no evidence of reduction in rates of death alone or BPD in infants treated with iNO compared to controls [68]. An individualized patient data meta-analysis of randomized trials also found that routine use of iNO for treatment of respiratory failure cannot be recommended [80]. The variable results and difficulty in interpretation of the numerous trials prompted an NIH consensus development conference which concluded that current evidence does not support use of iNO in early routine, early rescue, or later rescue regimens in the care of premature infants <34 weeks [81]. Future trials to define the optimal dose, timing, and duration of iNO therapy in prevention on BPD are warranted and are ongoing at the time of this review.

11. Other Potential Therapies

11.1. Mesenchymal Stem Cell Therapy. The therapeutic potential of stem cells is currently explored for a variety of disorders. Intrinsic qualities of mesenchymal stem cells such as their capacity to respond, migrate, and replace damaged tissue make them an attractive candidate for prevention and repair of neonatal lung injury. In animal models, bone marrow-derived mesenchymal stem cells (BMSCs) have been shown to ameliorate injury in multiple organs including heart, brain, kidney, and lung [82–85]. In neonatal rodent models of BPD, allogenic BMSCs have been shown to prevent lung injury and lung inflammation [84–86]. This protection was observed despite a very low level of BMSC engraftment in the lungs. In fact, even more profound improvement in alveolar simplification and vascular injury was seen after delivery of BMSC-conditioned media indicating that a paracrine mechanism is likely involved [84]. Further studies in animal models of BPD are needed to address whether BMSCs can provide protection by a paracrine immunomodulatory response leading to release of specific growth factors and anti-inflammatory molecules [86].

12. Conclusion

Well-conducted clinical trials and meta-analyses have demonstrated a lack of significant impact of several pharmacologic therapies [87]. Despite this, many pharmacologic therapies are currently practiced because of transient beneficial effects and lack of alternatives. As our understanding of the complex and multifactorial pathophysiology of BPD improves, it becomes clear that targeting individual pathways is unlikely to have a significant impact on outcome. A multidrug approach addressing several pathways simultaneously may have a more significant impact on the incidence and progression of the disease. We need to continue to work to understand the basic mechanisms of neonatal lung development, injury, and repair. In addition, targeted therapeutic approaches based on host factors and specific patient genetic and epigenetic makeup may allow better therapeutic choices. Some prediction tools have been developed based on risk factors to help provide prognostic information and facilitate identification of infants who may benefit from therapies available [88]. Continued clinical practice optimization with minimization of ventilator-induced lung injury, oxygen toxicity, and infection as well as continued optimization of nutrition should also continue to be pursued. As we gain new insight into the disease process and evaluate novel approaches, it is essential to focus not only on short-term outcomes and safety profiles but also on long-term pulmonary and neurodevelopmental outcomes.

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Research Article

Factors Affecting the Weaning from Nasal CPAP in Preterm Neonates

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Objective. Identification of the weight and postmenstrual age (PMA) at successful weaning of NCPAP in preterm neonates and the factors influencing the successful wean. *Study Design*. Retrospective review of 454 neonates ≤32 weeks of gestational age (GA) who were placed on NCPAP and successfully weaned to room air was performed. *Results*. Neonates had a mean birth weight (BW) of 1357 ± 392 grams with a mean GA of 29.3 ± 2.2 weeks. Neonates were weaned off NCPAP at mean weight of 1611 ± 432 grams and mean PMA of 32.9 ± 2.4 weeks. Univariate analysis showed that chorioamnionitis, intubation, surfactant use, PDA, sepsis/NEC, anemia, apnea, GER and IVH were significantly associated with the time to NCPAP wean. On multivariate analysis, among neonates that were intubated, BW was the only significant factor ($P < 0.001$) that was inversely related to time to successful NCPAP wean. Amongst non-intubated neonates, along with BW ($P < 0.01$), chorioamnionitis ($P < 0.01$), anemia ($P < 0.0001$), and GER ($P < 0.02$) played a significant role in weaning from NCPAP. *Conclusion*. Neonates were weaned off NCPAP at mean weight of 1611 ± 432 grams and mean PMA of 32.9 ± 2.4 weeks. BW significantly affects weaning among intubated and non-intubated neonates, though in neonates who were never intubated chorioamnionitis, anemia and GER also significantly affected the duration on NCPAP.

1. Introduction

Treatment of neonatal respiratory distress syndrome (RDS) with intermittent positive pressure ventilation (IPPV) has been associated with significant pulmonary morbidity. Studies have shown that this morbidity can be reduced by use of nasal continuous positive airway pressure (NCPAP) [1–4], leading to increased use of NCPAP for the management of RDS in preterm neonates in recent years. Multiple studies have also demonstrated that NCPAP is a safe treatment modality with no increase in short-term [5–10] and long-term [11, 12] morbidities. It also has other beneficial effects including induction of lung growth [13]. Although NCPAP has been used more routinely, there is paucity of information on factors affecting the weaning process such as weight and PMA at the time of successful weaning and the factors that influence the weaning process [14, 15].

Recently, studies have been conducted to evaluate the methods of NCPAP wean used at several neonatal intensive care units (NICUs). These identified a lack of agreement on the method of NCPAP wean used at various NICUs with only 6% of the participating NICUs having written guidelines regarding NCPAP wean. The start of the NCPAP weaning was frequently arbitrarily determined by healthcare providers (physicians, nurses, and respiratory technicians). There was variability in the method of weaning from NCPAP, which was attempted either by gradually increasing the time of NCPAP, by reducing pressure, or by using both methods

[16, 17]. Additionally, these surveys did not identify the age, weight, or associated clinical comorbidities, which may affect successful weaning from NCPAP in preterm neonates. A recent Cochrane review on weaning from NCPAP in preterm neonates also highlighted the lack of information available on the weaning from NCPAP [18].

Given this paucity of information, the objective of our study was to identify the PMA and weight at which one can successfully wean preterm neonates born ≤32 weeks of gestational age off the NCPAP and the comorbidities that may influence the success of NCPAP weaning.

2. Materials and Methods

2.1. Patients. A retrospective chart review was conducted on all babies born at GA of ≤32 weeks who were admitted to the NICU at Maimonides Infants and Children's Hospital, Brooklyn, between 1st of January 2003 and 31st of December 2007. This study was approved by the institutional review board at Maimonides Medical Center and was conducted in compliance with Health Insurance Portability and Accountability Act regulations.

There were 648 babies who were born at ≤32 weeks of GA and admitted to the NICU during the study period. We excluded all neonates who were stable in room air and did not need any respiratory support ($n = 103$) and those who died or transferred out while intubated or before they could be weaned off NCPAP ($n = 85$). Those who were placed on nasal cannula before meeting the criteria of successful weaning from NCPAP ($n = 6$) were also excluded. Nasal SIMV was not used in our nursery during the study period. Thus, data from 454 eligible neonates was analyzed for the study.

The primary variables studied were BW, GA, ethnicity, and gender. Additionally, weights and the PMA at the following four time points were obtained: (1) when the neonates were placed on NCPAP, (2) when they reached FiO_2 of 0.21 on NCPAP, (3) when weaning from NCPAP was initiated, and (4) when the NCPAP was successfully weaned off. The association of antenatal factors and postnatal comorbidities with the time to NCPAP weaning was also studied. Antenatal factors such as use of antenatal steroids (complete course) and magnesium sulphate, presence of chorioamnionitis, preeclampsia (blood pressure of more than 140/90 with proteinuria), and intrauterine growth retardation (IUGR) (less than 3rd percentile on the growth curve) were analyzed. Postnatal factors included in the analysis were intubation prior to weaning from NCPAP, use of surfactant, the presence of patent ductus arteriosus (PDA), diagnosed in first week (confirmed by echocardiography), anemia (hematocrit of <30 1 week prior to the initiation of NCPAP weaning), GER (diagnosed clinically and treated with H_2 blocker or proton pump inhibitor), apnea (cessation of respiration for >20 seconds associated with bradycardia or cyanosis) >2 in 12 hours or >3 in 24 hours with, at least, one requiring bag and mask ventilation, and presence of intraventricular hemorrhage (IVH) (diagnosed by ultrasound). In addition, occurrence of sepsis/necrotizing enterocolitis (NEC) (culture positive or radiologically proven) was also included in the analysis. These two clinical conditions were analyzed together as both similarly affect the respiratory system and hence the duration time on NCPAP through the effect of inflammatory mediators on the lungs. Caffeine was exclusively used to treat neonates diagnosed with apnea.

2.2. Respiratory Management. A uniform method of respiratory management has been practiced in our NICU [19, 20] for over a decade. In summary, all spontaneously breathing neonates with respiratory distress are placed on bubble NCPAP using the Hudson RCI nasal prongs (Hudson Respiratory Care, Temecula, California, USA) with 5 cm H_2O pressure within first 10 minutes of life irrespective of GA and BW of the neonate. Neonates who are not breathing spontaneously at birth or fail a trial of NCPAP are intubated. Failure of NCPAP is defined as increased work of breathing determined clinically by persistent tachypnea (>60/minute for >2 hours) and marked retractions, apnea as defined above, abnormal blood gases (2 arterial samples >2 hours apart) low pH < 7.2, $PaCO_2$ > 65 mm of Hg, and PaO_2= of <50 mm of Hg with FiO_2 of ≥0.4. Surfactant is only used as rescue treatment. The peak end expiratory pressure is kept at 5 cm H_2O during the weaning process.

NCPAP weaning is initiated when the neonate is clinically stable on room air NCPAP for 48 hours. When neonates are weaned off NCPAP, special attention is paid to upper airway suctioning and to keeping the neck in a neutral position to prevent excessive flexion or extension. Success of weaning from NCPAP is defined as the baby being stable in room air without any respiratory support for 7 days.

2.3. Statistical Analysis. Statistical analysis was done using STATA version 10 (StataCorp LP. College Station, Tex, USA). Continuous variables such as BW, GA, PMA at various time points of NCPAP weaning, and hematocrits were evaluated for normality. While BW was normally distributed, GA was not. As expected, those born at a younger GA were on NCPAP for a longer duration. To accommodate to this, we used PMA at complete weaning of NCPAP as the outcome variable of interest, since this was normally distributed in our sample. Univariate analysis was conducted using the *t*-test or analysis of variance for continuous variables and chi-square test for categorical variables to identify the association of clinical variables with the PMA at NCPAP weaning. To study the association of ethnicity with NCPAP weaning, Caucasians were used as the reference group. The Spearman correlation was used to study the association of NCPAP weaning with continuous variables such as hematocrit levels.

Linear regression analysis was done to identify the significance of the association of the variables identified by univariate analysis on the primary outcome variable of interest, that is, the PMA at successful weaning from NCPAP when adjusted for other clinical variables. Variables of epidemiological significance such as gender were retained in the model even though they did not reach statistical significance in univariate analysis. We identified a significant interaction between birth weight and intubation. To account for this, a stratified analysis was performed, based on intubation status, as shown in Table 4. In addition, there was significant collinearity between intubation and surfactant, PDA,

Table 1: Demographic and clinical data of the study population.

Demographic/clinical characteristic	Full cohort $n = 454$ n (%)	Nonintubated $n = 326$ n (%)	Intubated $n = 128$ n (%)	P value
Male	242 (53.3)	179 (54.9)	63 (49.2)	0.29
Ethnicity				
White	133 (29.3)	93 (28.5)	40 (31.3)	0.59
African Americans	79 (17.4)	58 (17.8)	21 (16.4)	
Hispanics	108 (23.8)	83 (25.5)	25 (19.5)	
Asians	88 (19.4)	63 (19.1)	26 (20.3)	
Multiracial	46 (10.1)	30 (9.2)	16 (12.5)	
Antenatal steroids	361(79.5)	257 (78.8)	104 (81.3)	0.56
Chorioamnionitis	21 (4.6)	14 (4.5)	7 (5.5)	0.58
Preeclampsia	72 (15.9)	54 (16.6)	18 (14.1)	0.50
Magnesium sulphate use	203 (44.7)	135 (41.1)	68 (53.1)	0.02
IUGR	19 (4.2)	13 (3.9)	6 (4.7)	0.74
Intubation	128 (28.3)			
Surfactant	89 (19.6)	0 (0)	89 (69.5)	
IVH	69 (15.1)	26 (8.0)	43 (33.6)	<0.001
PDA	167 (36.9)	19 (5.8)	66 (51.6)	<0.0001
Sepsis/NEC	40 (8.8)	20 (6.1)	20 (15.6)	<0.001
Anemia	273 (80.1)	150 (46.0)	123 (96.0)	<0.0001
Apnea	100 (22.3)	45 (13.8)	55 (42.9)	<0.0001
GE reflux	29 (6.9)	7 (2.1)	22 (17.2)	<0.001
BPD	50	7 (2.1)	43 (33.6)	<0.001

Abbreviations: IUGR: intrauterine growth retardation, PDA: patent ductus arteriosus, IVH: intraventricular hemorhage, NEC: necrotizing enterocolitis, GE reflux: gastroesophageal reflux.

and apnea. For this reason, these variables were not included in the final stratified model. Regression diagnostics were performed to ensure that assumptions of linear regression analysis were not violated.

3. Results

For the entire study population, the mean BW was 1357 ± 392 grams and mean GA was 29.3 ± 2.2 weeks. Demographic and clinical data of the study cohort as a whole and when stratified by intubation is shown in Table 1. There was no effect of gender or of ethnicity on the PMA at successful NCPAP weaning.

The weights and PMA of the neonates at various NCPAP time points are shown in Table 2. The mean GA of those requiring intubation was 27.3 ± 2.1 weeks and of those not requiring intubation was 30.1 ± 1.7 weeks ($P < 0.0001$). There were significant differences between those who were intubated and those who did not require intubation in the PMA and their weights at various NCPAP time points.

As shown in Figures 1 and 2, there was a significant inverse correlation between GA ($r = -0.11$, $P < 0.0001$) and BW ($r = -0.12$, $P < 0.0001$) to PMA at successful NCPAP weaning. The beta for the regression line for GA was -0.4; hence, the duration on NCPAP decreased by 0.4 weeks for every week increase in GA. Similarly the beta for the regression line for BW was -0.21; the duration of NCPAP decreased by 0.2 weeks for every 100 grams increase in BW.

Univariate analysis of clinical comorbidities with PMA at successful NCPAP weaning is shown in Table 3. There was a significant association of PMA at successful NCPAP weaning with chorioamnionitis, intubation, and comorbidities such as PDA, sepsis/NEC, anemia, apnea, GER, and IVH. There was significant association between PDA, apnea, and surfactant use and successful NCPAP weaning in our study, but since there was collinearity between these variables and intubation, we used intubation as a marker for these variables in multivariate analysis. In addition to BW and GA, successful weaning had a significant inverse correlation with hematocrit ($r = -0.44$, $P < 0.001$) and positive correlation with the severity of IVH ($r = 0.34$, $P < 0.0001$).

As shown in Table 4, in multivariate analysis, BW, chorioamnionitis, anemia, GER, and IVH were independent predictors for successful NCPAP weaning. In the stratified model, among those neonates who were not intubated, BW, chorioamnionitis, anemia, and GER remained independent predictors of successful NCPAP weaning. On the other hand, among those who were intubated prior to weaning, BW was the only independent predictor of successful NCPAP weaning with the other comorbid conditions not reaching statistical significance. In the whole cohort, length of stay on NCPAP increased by 1.1 weeks in those who had

Table 2: Weight (grams) and postmenstrual age (PMA in weeks) at various NCPAP time points, for the entire cohort and for subgroups stratified by intubation.

	Full cohort ($n = 454$)		Nonintubated ($n = 326$)		Intubation ($n = 128$)	
	Weight	PMA	Weight	PMA	Weight	PMA
At start of NCPAP	1356 ± 392	29.6 ± 2.1	1480 ± 346	30.3 ± 1.7	1037 ± 315*	27.9±2.1***
Reaching 0.21 FiO_2 NCPAP	1342 ± 377	30.1 ± 2.1	1441 ± 344	30.5 ± 1.7	1089 ± 339*	29 ± 2.6*
Initiation of NCPAP weaning	1492 ± 376	31.9 ± 2.2	1462 ± 345	31.3 ± 1.4	1570 ± 438*	33.2 ± 2.9*
Successful NCPAP weaning	1611 ± 432	32.9 ± 2.5	1580 ± 381	32.1 ± 1.7	1869 ± 484**	35 ± 2.9**

* $P < 0.01$, ** $P < 0.001$, *** $P < 0.0001$ when the weights and PMA of intubated neonates were compared to those nonintubated.

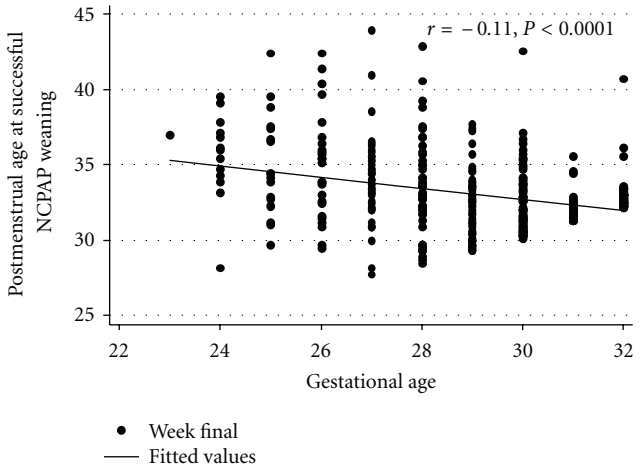

Figure 1: Correlation between GA and PMA at successful NCPAP weaning.

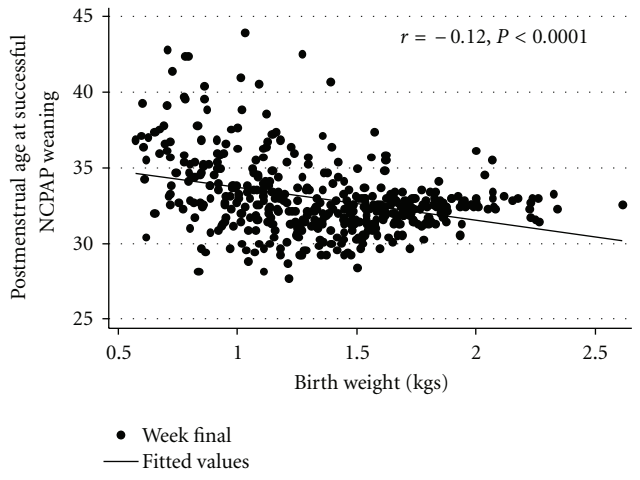

Figure 2: Correlation between BW and PMA at successful NCPAP weaning.

chorioamnionitis, 1 week in those who had anemia, and 1.9 weeks in those who had GER.

4. Discussion

We found that GA and BW were strongly correlated with the duration of NCPAP in neonates born less than 32 weeks of gestation but there was no association with ethnicity or gender. These findings differ from previous studies that have demonstrated links between ethnicity and the severity of RDS [21]. These differences in the observation may be due to the relatively small sample size of our study as gender- and ethnicity-specific difference in disease severity have been elucidated in large-population-based epidemiological studies.

While several factors were found to be associated with increased time on NCPAP, we identified that there was a difference in their role among neonates that were intubated and those who were not intubated. The time to successful NCPAP weaning was longer among nonintubated preterm neonates who had evidence of maternal chorioamnionitis, anemia, and gastroesophageal reflux. However, among those neonates who were intubated, weaning from NCPAP was not associated with any of these factors.

In the nonintubated neonates, maternal chorioamnionitis was associated with increased length of time on NCPAP, which may be due to the injury caused by inflammatory mediators to the immature lungs, predisposing them to develop chronic lung disease [22–24]. The effects of anemia on the duration of NCPAP are likely due to decrease in oxygen delivery and increase in cardiac load and work of breathing. Studies have linked anemia with failure of extubation in children and adults, but similar findings have not been reported with weaning of NCPAP [25]. The effect of GER on failure to wean off NCPAP could be related to its association with increased incidence and severity of apneas related to acid reflux and associated lung inflammation related to frequent aspirations [26]. However, prior studies have failed to demonstrate this association [27]. We also found preterm neonates with GER had a higher incidence of BPD. This has been previously reported and may further explain the association between GER and the longer duration of NCPAP use [28]. While we have identified these associations, further studies are needed to corroborate these findings since they have direct clinical application and significance on management of preterm neonates. However, the associations identified in our study highlight the need for appropriate identification and management of these comorbid conditions to facilitate early weaning of NCPAP.

The delayed weaning from NCPAP in the intubated preterm neonates not only may be related to the immaturity of the lungs (as the intubated preterm neonates had lower gestational age), but could also be due to the ventilator-induced lung injury associated with intubation and positive-pressure ventilation. The process of intubation not only

Table 3: Effect of clinical factors on PMA in weeks at successful NCPAP weaning.

	Present*	Absent*	*P*-value
Antenatal steroids	32.9±2.5	32.7±2.2	$P = 0.38$
Chorioamnionitis	34.1±2.8	32.9±2.4	$P < 0.02$
Preeclampsia	32.5±2.2	33±2.5	$P = 0.14$
Magnesium sulphate use	33.1±2.7	32.8±2.2	$P = 0.26$
IUGR	33.1±2.2	32.9± 2.5	$P = 0.72$
Intubation	35.0±2.9	32.1±1.7	$P < 0.00001$
PDA	34.2±2.9	32.2±1.7	$P < 0.0001$
Sepsis/NEC	34.2± 2.5	32.8±2.4	$P < 0.0001$
Anemia	33.7±2.8	31.8±1.2	$P < 0.0001$
Apnea	33.9±2.6	32.7±2.3	$P < 0.0001$
GE reflux	35.6± 3.5	32.8±2.3	$P < 0.00001$
IVH (grades3/4)	34.5±3.4	32.6±2.1	$P < 0.0001$

* PMA is reported as mean ±SD.
Abbreviations: IUGR: intrauterine growth retardation, PDA: patent ductus arteriosus, NEC: necrotizing enterocolitis, GE Reflux: gastroesophageal reflux, IVH: intraventricular hemorhage.

Table 4: Multivariate analysis for PMA at successful NCPAP weaning and significant predictor variables, analysis done for the group as a whole and when stratified by intubation.

	Full cohort ($n = 454$)			Nonintubated ($n = 326$)			Intubated ($n = 128$)		
	Beta	95% CI	*P* value	Beta	95% CI	*P* value	Beta	95% CI	*P* value
BW	−0.90	−1.50–0.28	0.004	−0.76	−0.17–1.30	0.01	−2.50	−4.02–0.99	0.001
Gender	−0.14	−0.54–0.26	0.5	−0.15	−0.51–0.20	0.39	−0.13	−1.10–0.85	0.8
Chorioamnionitis	1.14	0.19–2.10	<0.01	0.72	0.16–1.60	0.01	0.95	−1.18–3.08	0.38
Sepsis/NEC	0.67	−0.05–1.38	0.06	0.71	−0.03–1.50	0.06	0.21	−1.12–1.54	0.75
Anemia	1.05	0.56–1.55	<.0001	0.91	0.50–1.30	<.001	0.61	−2.10–3.40	0.69
IVH	1.14	0.57–1.72	<.01	0.52	−0.13–1.18	0.1	0.80	−0.20–1.82	0.12
GE reflux	1.99	1.16–2.82	<.0001	1.44	0.23–2.65	.02	1.23	−0.06–2.52	0.06

Abbreviations: BW: birth weight, IVH: intraventricular hemmorhage, NEC: necrotizing enterocolitis, GE Reflux: gastroesophageal reflux.

increases the chances of hemodynamic instability [29] but also bridges the unsterile upper airway to that of the lower airway leading to increased incidence of colonization and infection of the lower airways and lungs causing lung injury [30]. Positive-pressure ventilation also causes trauma to the lungs by multiple mechanisms such as barotrauma, volutrauma, atelectrauma, and biotrauma [31]. In multivariate analysis, BW was the only significant factor determining time for weaning among those preterm neonates who were intubated with no association identified with the comorbid conditions that were found to be significant in those who were not intubated. It may be hypothesized that the role of these comorbidities was masked by the immaturity of the lungs and severity of ventilation-induced injury in the intubated neonates. Furthermore, intubated neonates were on NCPAP with FiO_2 of 0.21 longer than their nonintubated counterparts. As intubation and ventilation are associated with pulmonary injury and NCPAP helps in lung growth and repair [13], intubated neonates took longer to reach a point at which they could be weaned off NCPAP even when they reached room air NCPAP. However this is the first study to identify differences in the association of clinical morbidities with NCPAP weaning among neonates by intubation status. Hence future studies are needed to corroborate our findings.

We recognize that caffeine use was limited to the preterm neonates with significant apnea. These neonates were on NCPAP for a longer duration than those without apneas. In keeping with the findings of Schmidt et.al. [32], if all our preterm neonates had received caffeine, the difference between the duration of NCPAP in the nonintubated and the intubated neonates would have been expected to more pronounced than that observed, as the nonintubated neonates would be able to come off NCPAP even earlier.

There are certain limitations to this study, specifically, those inherent to retrospective analysis and those related to the information derived from a single center. One feature which is unique to our unit is the lower incidence of bronchopulmonary dysplasia (BPD), despite a similar incidence of RDS, compared to other centers in the Vermont Oxford database. The average incidence of BPD in less than 1500 gram preterm neonates in our NICU varied from 7.4% to 10.5% as compared to the 26.7% to 29.7% in the database during the 5-year study period. However, as NCPAP has been associated with lower incidence of BPD rates [33], we

attribute these differences to the higher use of NCPAP in our NICU as compared to other centers. Further, the diagnosis of GER was made clinically and not by pH probe, but if a pH probe study was performed, more cases of subclinical GER would be diagnosed likely making the association of weaning failure and GER even stronger. Moreover, since anemia was significantly related to the success of NCPAP weaning, transfusions may have impacted the success of weaning. However, as the transfusion threshold was the same for all the neonates prior to the weaning of NCPAP, irrespective of the intubation status, it was likely not associated with any misclassification bias. Additionally, we did not use nasal SIMV during NCPAP weaning. We recognize that the judicious use of this technique might have reduced the need of ventilation and may have decreased the time on NCPAP as suggested by a recent review [34]. Another limitation in this study was the inability to determine which method of weaning (sudden removal of NCPAP, gradual weaning by decreasing pressure or by gradually increasing time off NCPAP) was better in getting the neonates weaned from the NCPAP earlier or if any factors studied had different relationship with the weaning techniques. This was difficult to evaluate due to the retrospective nature of the study. Further studies are needed to evaluate the best method to wean preterm neonates off NCPAP.

In conclusion, our findings suggest that in preterm neonates, NCPAP can be successfully weaned off at a mean PMA of 32.9 ± 2.4 weeks and weight of 1611 ± 432 grams. There was an inverse relationship between time to successful NCPAP weaning and BW. In addition, among those neonates who were not intubated, prevention of maternal chorioamnionitis, identification and treatment of anemia and GER may reduce the time on NCPAP. Our findings provide neonatal health care providers clinical information on successful NCPAP weaning that may be used to initiate wean and help in decreasing the number of weaning failures. This information could also be used to counsel parents on the time when neonates could be expected to be successfully weaned from NCPAP. As our findings are from a single clinical center, future multicenter trials are needed to study whether these factors uniformly influence NCPAP wean in different neonatal intensive care units.

Abbreviations

PMA: Postmenstrual age
GA: Gestational age
BW: Birth weight
NCPAP: Nasal continuous positive airway pressure
GER: Gastro-esophageal reflux
RDS: Respiratory distress syndrome
IPPV: Intermittent positive pressure ventilation
NICU: Neonatal intensive care unit
IUGR: Intra-uterine growth retardation
PDA: Patent ductus arteriosus
NEC: Necrotizing enterocolitis
IVH: Intraventricular hemorrhage
BPD: Broncho-pulmonary dysplasia.

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Clinical Study

A Population-Based Study of Meconium Aspiration Syndrome in Neonates Born between 37 and 43 Weeks of Gestation

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The epidemiology of meconium aspiration syndrome (MAS) in term neonates is described in a population-based retrospective study of data recorded for all births from 2000 to 2007 in a French region (Burgundy). Of the 132 884 eligible term newborns, the rate of meconium-stained amniotic fluid (MSAF) was 7.93%. The prevalence of severe MAS was 0.067% in the overall population. MAS rate was 0.11% at 37-38 weeks of gestation (WG), 0.20% at 39–41 WG, and 0.49% at 42-43 WG. Factors independently associated with severe MAS were identified by a case-control study, that is, thick meconium amniotic fluid, fetal tachycardia, Apgar score ≤3 at 1 minute, and birth in a level III facility. Our results confirm the high prevalence of MSAF after 37 WG but also show the low frequency of severe MAS in a period corresponding to the new international recommendations on the management of birth with MSAF.

1. Introduction

Meconium aspiration syndrome (MAS) is an infrequent but life-threatening respiratory disease affecting some of the infants born through meconium-stained amniotic fluid (MSAF).

MAS may be a severe condition as 30 to 50% of MAS required mechanical ventilation or continuous positive airway pressure (CPAP) [1, 2].

MAS is frequently associated with fetal hypoxia which promotes meconium discharge in amniotic fluid, gasping and aspiration of MSAF, and also changes in the vascular muscular media of pulmonary arteries of the fetus [3, 4].

In the early 2000, the prevalence of MAS ranged from 0.20% to 0.54% in the general population [5–7] and from 1.0% to 6.8% in infants born through MSAF [3, 5–7]. A review of ten reports published from 1990 to 1998 showed a combined incidence of 13.1% for MSAF, 0.52% of MAS, 4.2% of MAS among MSAF, and 49.7% of MAS requiring ventilatory support with a 4.6% mortality rate [6].

However, large population-based studies were scarce and suggested a lower incidence of MAS: the national US birth cohort study conducted on the basis of singleton term non-Hispanic white live births (1995–2001) showed that the rate of MAS markedly increased with gestational age (GA), that is, from 0.10% at 37 weeks gestation (WG) to 0.22 and 0.31% at 40 and 41 WG, respectively [8]. The prevalence of MAS could be extrapolated to 0.18% in this population of term infants. In Australia, the rate of MAS requiring mechanical ventilation in level III units ranged between 0.024 to 0.046% at 36–40 WG and then increased to 0.080% at 41 WG and 0.14% at 42 WG [9]. In France, the prevalence of mechanically ventilated MAS was estimated to 0.043% by a retrospective national survey among neonates born in 2000-2001 [10].

Previous studies identified several risk factors of MAS that is, fetal compromise indicated by abnormalities of fetal heart rate tracings and/or poor Apgar score [1, 11–16] and/or low cord pH [5, 17]; Cesarean delivery [1, 18]; ethnicity (black Americans, Africans, Pacific Islanders); advanced gestation [15, 19, 20]. However, studies based on the global population did not specifically address the determination of risk factors of severe MAS among infants born through MSAF. It is worthy to note that regionalization of perinatal care

concentrated high risk pregnancies in level III facilities, a condition representing a potential bias in assessing prevalence of severe MAS and identification of risk factors.

Therefore, a population-based study was designed to confirm the low prevalence of severe MAS and identify risk factors of severe MAS among term infants born in MSAF.

2. Methods

The database of the Burgundy perinatal network was studied for the years 2000–2007. The Burgundy perinatal database is a voluntary collaboration between all 18 public and private hospitals in Burgundy (level III: 1; level II: 7; level I: 10) [21, 22]. The database which was set up with the approval of the National Committee of Informatics and Liberty includes all mother-infant pairs. Perinatal data are recorded at the time of neonatal discharge from maternities or neonatal units. Procedures are established to ensure quality of the recorded data, including standardized definitions, guidelines for coding, and validation of data coherence by specific softwares [21, 22].

All live births are eligible if their GA was ≥37 WG' estimated GA. Exclusion criteria included severe congenital malformations, chromosomal abnormalities, congenital neuromuscular diseases, and metabolic diseases.

All cases of MSAF and MAS were identified in the perinatal database. Severe MAS (i.e., treated by mechanical ventilation and/or continuous positive airway pressure) and their controls were confirmed when the medical records were systematically reviewed and abstracted by an independent neonatologist assessor (C.R or C.F). The diagnosis of MAS was established according to diagnostic criteria from Rubaltelli et al. [23], that is, respiratory distress with elevated oxygen dependence; presence of meconium in amniotic fluid; chest radiograms with massive bilateral patchy infiltrates with or without pleural fluid. For each patient, the type MSAF was qualified as "thin" when the fluid was just tinted yellowish or slightly greenish, "moderate" when it was really greenish, but fluid and "thick" when it was green and thick.

The GA, in completed weeks, was assessed on the basis of the mother's last menstrual period as confirmed or modified where necessary by routine early antenatal ultrasound examination. Owing to the low prevalence of MAS, a case/control study appeared optimal. For each case of severe MAS, 3 controls born in MSAF without any respiratory distress at birth were obtained from the regional database. Cases and controls were paired according to GA assuming a preponderant role of GA in MAS incidence [8, 9, 24–28]. The recorded variables are those shown in Table 2. Fetal heart rate recordings were precisely reviewed and classified according to French guidelines (fetal tachycardia, bradycardia, decelerations, decreased variability) [29].

2.1. Statistics. Quantitative data were presented as a mean and standard deviation (SD), and compared by one-way analysis of variance or, if normality or homoscedasticity assumptions, were violated Mann-Whitney U-test. Qualitative data were presented as percentages and compared using Pearson Chi Square or, in the case of very rare conditions, Fisher's exact test.

Secondly, a conditional logistic regression was used to determine significant independent variables associated with an increased risk of severe MAS. The model was adjusted for amniotic fluid, Apgar score ≤3 at 1 min, level of birth place, mode of delivery, insufficient followup during pregnancy, and tachycardia or bradycardia on FHR recordings. A P value below 0.05, for a 2-tailed Wald test, was considered as statistically significant. First-order interactions were systematically tested by a 2-tailed Wald test and excluded from the model if they did not reach statistical significance at the 0.05 level. Adjusted odds ratio (OR) and their 95% confidence intervals (CI) were calculated.

Statistical analyses were performed using SAS 9.2 (SAS Institute Inc) and Stata 8.0 (StataCorp LP) packages.

3. Results

The Burgundy perinatal database collected a total of 133 087 births with GA ≥37 WG from the period beginning January 1st, 2000 and ending on December 31st, 2007. Of these births 203 had exclusion criteria and 10 540 of the 132 884 eligible neonates (7.93%) were delivered within MSAF (thin, moderate, or thick).

The incidence of MSAF linearly increased with GA (Figure 1). The rate of MSAF was 3.52% at 37-38 WG versus 9.07% at 39–41 WG (OR = 2.74 [2.56 to 2.92, $P < 0.0001$]) and 14.37% at 42-43 WG (OR = 4.60 [4.03 to 5.26; $P < 0.001$]).

The regional database identified 241 neonates with MAS. The prevalence of MAS were 0.18% of the overall population. The incidence of MAS markedly increased with GA after 39 WG (Figure 2). The rates of MAS were 0.11% at 37-38 wks versus 0.20% at 39–41 wks (OR = 1.86 [1.27 to 2.72, $P = 0.0013$]) and 0.49% at 42-43 wks (OR = 4.65 [2.34 to 9.27; $P < 0.0001$]).

The odds ratios of MSAF and MAS at each gestational age are indicated in Table 1.

The global prevalence of MAS in neonates born with MSAF was 2.29% and did not significantly change with GA (Figure 1).

Among the 241 MAS, treatment modalities were oxygen alone in 152 (63.1%), nasal CPAP without mechanical ventilation in 3 (1.2%), conventional ventilation without high frequency oscillation (HFO) in 69 (28.6%), HFO in 17 (7.1%). Therefore, severe MAS (i.e., MAS treated by mechanical ventilation and/or nasal CPAP) was identified in 89 neonates. The prevalence of severe MAS was 0.067% of the overall population, 0.84% of neonates born through MSAF, and 36.9% of MAS.

Amongst the 89 severe MAS the median of duration of mechanical ventilation (conventional ventilation and HFO) was 2.0 days (1.0–5.0). Surfactant was given to 34 and antibiotics to 79 of the 89 infants with severe MAS (38.2% and 88.9%, resp.). Nitric oxide inhalation and ECMO were used in 15 (16.8%) and 2 (2.2%) infants, respectively. The neonatal course was associated with persistent pulmonary hypertension of the neonate in 14 (15.7%), air leaks in 10

Table 1: Odds ratios (95% CI; P value) of meconium-stained amniotic fluid (MSAF) and meconium aspiration syndrome (MAS) in neonates born between 38 and 43 WG compared to neonates born at 37 WG.

	38 WG	39 WG	40 WG	41 WG	42 SA	43 WG
MSAF	1.11 [0.97, 1.28; $P = 0.13$]	1.94 [1.71, 2.20; $P < 0.0001$]	3.22 [2.84, 3.63; $P < 0.0001$]	4.08 [3.61, 4.62; $P < 0.0001$]	4.96 [4.20, 5.87; $P < 0.0001$]	5.29 [2.03, 13.8; $P = 0.0007$]
MAS	0.89 [0.42, 1.90; $P = 0.77$]	0.96 [0.48, 1.93; $P = 0.92$]	2.10 [1.09, 4.03; $P = 0.026$]	2.25 [1.16, 4.38; $P = 0.016$]	3.97 [1.65, 9.55; $P = 0.002$]	27.3 [3.40, 220; $P = 0.002$]

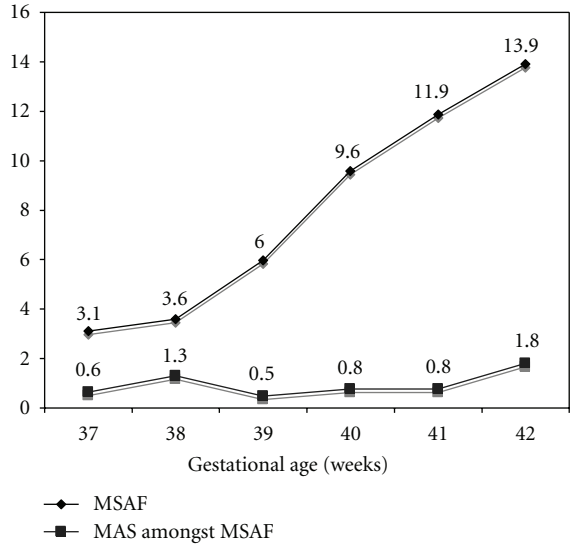

Figure 1: Rates of meconium-stained amniotic fluid (MSAF) in the global population and rate of meconium aspiration syndrome (MAS) amongst MSAF according to gestational age in term and postterm deliveries.

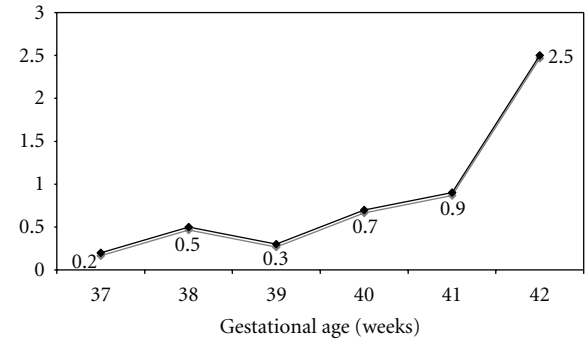

Figure 2: Rates of meconium aspiration syndrome (MAS) in the global population according to gestational age in term and post-term deliveries.

(11.4%), hypotension in 20 (22.5%), and late-onset neonatal infection in 4 (4.5%). Concerning thin versus moderate or thick meconium, mechanical ventilation duration was 1.0 (1.0–4.0) versus 2.0 (1.0–6.0; $P = 0.30$) days and death rate was 6.7% versus 8.5% ($P = 0.76$). There were 7 deaths (7.9%) of which 4 were related to severe ischemic encephalopathy and 3 were due to intractable pulmonary haemorrhage, sepsis, and multiple organ failure.

The 89 neonates with severe MAS were paired to 267 controls according to GA (40.0±1.2 weeks). Gestational age was 43 weeks in 6.7% of the neonates in this case-control study. Mean birthweight was 3388 ± 549 g in cases and 3329 ± 476 g in controls ($P = 0.33$).

Bivariate analysis identified significant risk factors associated to severe MAS (Table 2), that is, gestation with insufficient followup; birth place in a level III facility; delivery during day time; moderate and thick meconium; amnioinfusion; fetal tachycardia and fetal bradycardia; CS delivery; low Apgar score at 1 and 5 min; tracheal aspiration at birth and pediatrician intervention at birth.

The conditional logistic regression analysis identified independent variables significantly associated with an increased risk of severe MAS: amniotic fluid stained by moderate or thick meconium versus thin meconium (OR = 5.63 [2.52 to 12.6; $P < 0.0001$]); fetal tachycardia, (OR = 4.17 [1.27 to 3.7; $P = 0.019$]); Apgar score ≤3 at 1 min, (OR = 87.5 [18.9 to 405; $P < 0.0001$]); or birth in the level III facility in comparison with birth in the level II facilities (OR = 4.8 [2.0 to 11.6; $P = 0.0005$]).

4. Discussion

In this epidemiological study, MSAF is a frequent event accounting for 7.9% of all deliveries in non-preterm neonates. On the other hand, MAS is a rare event (0.18%) with a need for mechanical ventilation and/or nasal CPAP in approximately one-third of them as reported in other studies [1, 2, 6]. Avoiding mechanical ventilation by using nasal CPAP has probably a marginal role as only 1.2% of MAS are treated with this ventilatory mode. Goldsmith [2] recently highlighted that the optimum modes of ventilation for MAS are not known. He pointed out that high-frequency ventilation, inhaled nitric oxide, surfactant and extracorporeal membrane oxygenation are rarely required. Our series confirms this observation as only 12.0% of MAS required those treatments.

The overall incidence of MAS and severe MAS increases with GA as reported in recent population-based studies [8, 9]. The overall rates of MAS in the USA [8] and Burgundy are similar: 1.0 versus 1.1 per 1000 live births (‰) at 37 WG; 1.1 versus 1.0‰ at 38 WG; 1.5 versus 1.1‰ at 39 WG; 2.2 versus 2.4‰ at 40 WG, and 3.1 versus 2.6‰ at 41 WG. Furthermore the incidence of severe MAS recorded in Australia [9] at 41 WG (0.80‰) is close to the 0.67‰ observed at 39–41 WG in our series. So, our cohort of MAS can be regarded as representative of this pulmonary disease in the 2000 s in developed countries. It is interesting to note that the recent population based studies [8, 9] showed a low prevalence of MAS as compared to monocentric and multicentric studies

Table 2: Case-control comparison in a population of neonates with GA ≥37 weeks and born through MSAF. Cases are severe MAS (i.e., treated by mechanical ventilation and/or continuous positive airway pressure). Paired neonates without respiratory symptoms are controls.

	Cases $n = 89$	Controls $n = 267$	P value
Characteristics of the mother			
Age (years)	29.7 ± 5.8	28.9 ± 5.2	0.23
Nulliparity (%)	59.5	58.1	0.80
Past history of CS[a] (%)	7.95	7.87	0.97
Characteristics of pregnancy			
Multiple pregnancy (%)	0	1.5	0.24
Insufficient followup care (%)	8.99	0.75	<0.0001
Smoking (%)	21.6	18.5	0.52
Hypertension or preeclampsia (%)	2.28	4.91	0.28
Oligohydramnios (%)	4.5	3.4	0.62
Antenatal diagnosis of IUGR[b] (%)	1.12	2.64	0.40
Gestational diabetes (%)	2.28	6.0	0.16
Clinical chorioamnionitis (%)	0	0	1.0
GBS[c] vaginal carriage (%)	12.9	9.4	0.35
Placenta praevia (%)	0	0	1.0
Placental abruption (%)	0	0	1.0
Characteristics of delivery			
Cord abnormalities	23.6	26.7	0.53
PROM[d] (>12 hr)	4.6	9.7	0.13
Antenatal steroid therapy	2.2	0	0.25
Birth place:			
Level I (%)	16.8	11.2	
Level II (%)	49.5	77.	
Level III (%)	33.7	11.2	<0.0001
Day time delivery (%)	56.2	42.6	0.02
Induction of labor (%)	27.0	28.1	0.83
Meconium in amniotic fluid			
Thin (%)	33.7	76.4	<0.0001
Moderate (%)	55.1	22.8	
Thick (%)	11.2	0.78	
Amnioinfusion (%)	7.9	1.9	0.0067
Fetal Heart Rate (FHR):			
Tachycardia (%)	17.2	4.5	0.0001
Bradycardia (%)	49.4	32.9	0.0057
Presentation:			
Cephalic (%)	95.5	97.4	
Breech (%)	3.4	1.9	0.37
Other (%)	1.1	0.7	
Anesthesia			
(i) Spinal (%)	14.6	9.4	
(ii) Epidural (%)	69.7	67.0	
(iii) General (%)	2.2	3.0	0.29
(iv) No anesthesia (%)	13.5	20.6	
Mode of Delivery			
CS (%)	37.2	20.2	
Vaginal with manoeuvres (%)	17.9	17.9	
Vaginal without manoeuvres (%)	44.9	61.9	0.004
Obstetrical aspiration (%)	5.6	3	
Characteristics of neonates			
Sex ratio (% male)	47.2	48.3	0.85
Mean birthweight (g) (±SD)	3388 (±549)	3329 (±476)	0.33

Table 2: Continued.

	Cases $n = 89$	Controls $n = 267$	P value
BW[e] <10th perc. (%)	19.1	13.8	
BW ≥10th perc. ≤ 90th perc. (%)	67.4	77.6	
BW >90th perc. (%)	13.5	8.6	0.15
Apgar at 1 min ≤3 (%)	51.7	1.1	<0.0001
Apgar at 5 min ≤5 (%)	32.5	0.0	<0.0001
Tracheal aspiration at birth (%)	80.9	8.2	<0.0001
First care:			
Pediatrician (%)	73.4	28.5	<0.0001
Midwife (%)	23.6	71.5	

[a]CS: Cesarean section, [b]IUGR: Intrauterine growth restriction, [c]GBS: Group B Streptococcus, [d]PROM: prolonged rupture of membranes (>12 hours), [e]BW: birth weight.

usually conducted in level III facilities. Our series confirms the bias that could be induced by nonepidemiological studies of MAS incidence as it shows that birth in a level III facility is an independent risk factor of severe MAS. It can be speculated that regionalization of perinatal care concentrates high risk pregnancies in level III facilities and increases the risk for MAS. Finally, the case-control study suggested that the care in the Burgundy population with MSAF was characterized by low rates of amnioinfusion, obstetrical nasooropharyngeal aspiration and tracheal aspiration in infants born with MSAF but without MAS. This fits well with current recommendations [30] about management of infants born through MSAF: oronasopharyngeal suctioning before the delivery of the shoulders in infants born through MSAF is useless in the prevention of MAS; tracheal suctioning should be selectively applied to nonvigorous neonates born in MSAF according to the pivotal study of Wiswell et al. [31].

In this study the incidence of MAS is stable from 37 to 39 WG and increases afterwards particularly in infants born at 42-43 WG: the risk of MAS is approximately 4-fold and 27-fold at 42 WG and 43 WG in comparison to 37 WG.

However, the incidence of MAS in neonates born through MSAF does not vary significantly with GA. Similarly, population-based studies as well as nonpopulation-based studies showed that prolonged pregnancy (≥42 weeks) increases perinatal morbidity and mortality and greatly favours MSAF and MAS [7, 30, 32].

Some studies suggested that prevention of postterm pregnancy prevents severe MAS [33]. The earlier induction of labour (e.g., by 41 weeks) may prove to be beneficial for the prevention of the MAS as shown by Ross [34]. A recent Cochrane review [26] shows that a policy of labour induction is associated with a reduced incidence of MAS at both 41 completed WG (relative risk (RR) = 0.29 [0.12 to 0.68]) and 42 completed WG (RR = 0.66 [0.24 to 1.81]). However, a new randomised clinical trial [35] does not found any significant differences between induced and monitored postterm neonates regarding neonatal morbidity. New prospective randomised studies are required to establish whether labour induction reduces MAS incidence without promoting other respiratory diseases such as transient tachypnea of the newborn (TTN) or respiratory distress syndrome (RDS).

The low incidence of severe MAS and the preeminent role of GA on this incidence justified a case-control study [36] paired on GA. Amniotic fluid stained by moderately or markedly thick meconium, fetal tachycardia, and Apgar score ≤3 at 1 min promote severe MAS. Thick meconium is usually regarded as a common finding in severe meconium aspiration syndrome [3, 6, 19, 37], and most studies were focused on neonates born through moderate or thick MSAF. However, a lack of correlation between the severity of MAS and the thickness of meconium has been previously suggested by Ghidini and Spong [25] and Suresh and Sarkar [38]. Our series confirms this hypothesis as thick meconium is found in only 11% of severe MAS (1% of controls) while moderate and thin meconium concern 55% and 34% of severe MAS, respectively. Apgar score ≤3 at 1 min is the main risk factor as the relative risk is 87. Low Apgar score has been universally associated with MAS [1, 3, 6, 9, 11–16, 28, 32, 39, 40], and the role of fetal hypoxia has also been ascertained by elevated cord blood concentrations of erythropoietin in both MSAF [41] and MAS [32, 42].

It is well known that poor antenatal conditions are predominant in determining MAS. This point of view is reinforced as fetal tachycardia is another independent risk factor of severe MAS in this study. This observation has been made in many other studies, not reassuring fetal heart rate monitoring being widely associated with MAS [1, 11–16, 18, 43, 44]. However, contradicting data were obtained by Mitchell et al. [45] who concluded that FHR tracings are relatively poor predictors of the presence of fetal acidosis when amniotic fluid is meconium stained.

These overall results suggest that severe MAS is an antenatal disease thus justifying adapted antenatal care. Nowadays, identification of perinatal asphyxia remains a major endpoint of MAS prevention [33]. Guidelines of earlier fetal monitoring (e.g., by 40 WG) proved to be beneficial for the prevention of MAS [34].

Finally, our series failed to identify risk factors reported in some other studies, that is, nulliparity [32, 37], male gender [3], previous Cesarean section [16], and oligohydramnios [3]. Although our work is a population-based study in an entire French region with 1.8 millions inhabitants, there are only 89 cases of severe MAS over an 8-year period. A low sample size may have favored the low number of factors significantly associated with severe MAS.

5. Conclusion

Our series confirms the high prevalence of MSAF after 37 WG but also shows the low incidence of both MAS and severe MAS in a period corresponding to the implementation of the new international recommendations on the management of neonates born in MSAF [30].

The main risk factor of MSAF is GA but the incidence of MAS in neonates born in MSAF does not depend on GA. Our series indicates that moderate or thick amniotic fluid and fetal tachycardia may help to anticipate the need for neonatal resuscitation in delivery room whatever is GA. Further studies comparing perinatal factors associated with severe and nonsevere MAS could be useful to help clinicians in delivery room to anticipate severe MAS, a rare event which remains life threatening.

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Review Article

Advances in the Management of Meconium Aspiration Syndrome

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Meconium aspiration syndrome (MAS) is a common cause of severe respiratory distress in term infants, with an associated highly variable morbidity and mortality. MAS results from aspiration of meconium during intrauterine gasping or during the first few breaths. The pathophysiology of MAS is multifactorial and includes acute airway obstruction, surfactant dysfunction or inactivation, chemical pneumonitis with release of vasoconstrictive and inflammatory mediators, and persistent pulmonary hypertension of newborn (PPHN). This disorder can be life threatening, often complicated by respiratory failure, pulmonary air leaks, and PPHN. Approaches to the prevention of MAS have changed over time with collaboration between obstetricians and pediatricians forming the foundations for care. The use of surfactant and inhaled nitric oxide (iNO) has led to the decreased mortality and the need for extracorporeal membrane oxygenation (ECMO) use. In this paper, we review the current understanding of the pathophysiology and management of MAS.

1. Introduction

Meconium aspiration syndrome (MAS) is defined as respiratory distress in an infant born through meconium-stained amniotic fluid (MSAF) with characteristic radiological changes and whose symptoms cannot be otherwise explained [1]. Because meconium is rarely found in the amniotic fluid prior to 34 weeks' gestation, MAS is often a disease of the term and near-term infant and is associated with significant respiratory morbidity and mortality. Cleary and Wiswell [2] have proposed a severity criteria to define MAS: (a) mild MAS is a disease that requires less than 40% oxygen for less than 48 hours, (b) moderate MAS is a disease that requires more than 40% oxygen for more than 48 hours with no air leak, and (c) severe MAS is a disease that requires assisted ventilation for more than 48 hours and is often associated with PPHN. In this paper, we look at the current understanding of the pathogenesis and management of MAS.

2. Epidemiology of MAS

Meconium is a viscous sticky dark green substance containing gastrointestinal secretions, bile, bile acids, mucus, pancreatic juice, blood, swallowed vernix caseosa, lanugo, and cellular debris. Intrauterine hypoxia may cause passage of meconium in the amniotic fluid. MSAF is present in 8–20% of all deliveries [1–4], increasing to 23–52% after 42 weeks of gestation [5, 6]. Meconium aspiration may occur before birth, or during the birth process. About 2–9% of infants born through MSAF develop MAS [7–9]. About one-third of infants with MAS require intubation and mechanical ventilation [9].

Factors that promote the passage of meconium in utero include placental insufficiency, maternal hypertension, preeclampsia, oligohydramnios, and maternal drug abuse, especially of tobacco and cocaine. The risk of MAS is increased in black Americans, Africans, and Pacific Islanders [7, 10]. Factors associated with the development of MAS among infants with MSAF include thicker consistency of meconium, nonreassuring fetal heart tracing, fetal acidosis, cesarean delivery, meconium below the cords, infants who needed intubation at birth, and a low Apgar score [9, 11]. In the United States, the incidence of MAS decreased nearly fourfold from 5.8% to 1.5% between 1990–1992 and 1997-1998 and this was attributed to a 33% reduction in births at more than 41 weeks' gestation, more frequent diagnosis

of nonreassuring fetal heart rate patterns, and greater use of amnioinfusion [12]. MAS remains a serious problem in developing and newly industrialized countries, and MAS accounts for about 10% of all cases of respiratory failure with 39% mortality rate [13].

3. Pathophysiology of MAS

MAS results from aspiration of meconium during intrauterine gasping or during the first few breaths. Fetal hypoxic stress can stimulate colonic activity, resulting in the passage of meconium and also stimulates fetal gasping movements that result in meconium aspiration in-utero. Mounting evidence suggests that a chronic in utero insult may be responsible for most cases of severe MAS as opposed to an acute peripartum event [14, 15].

The pathophysiology of MAS is complex. Aspirated meconium can interfere with normal breathing by several mechanisms. The pathophysiologic mechanisms of hypoxemia in MAS include (a) acute airway obstruction, (b) surfactant dysfunction or inactivation, (c) chemical pneumonitis with release of vasoconstrictive and inflammatory mediators, and (d) PPHN with right-to-left extrapulmonary shunting. The common disturbances of lung function in MAS include hypoxemia and decreased lung compliance. Poor oxygenation is attributed to a combination of ventilation perfusion mismatching, intrapulmonary shunting related to regional atelectasis and extrapulmonary shunting related to PPHN.

Depending on the consistency and amount of meconium aspirated, meconium may lead to either partial or complete airway obstruction leading to hyperinflation or atelectasis of the alveoli. The gas trapped may rupture resulting in air leak syndromes such as pulmonary interstitial emphysema, pneumothorax, and pneumomediatinum.

Presence of meconium in the alveoli can inactivate the endogenous surfactant and decrease the production of surfactant proteins A and B [16, 17]. This causes atelectasis of the lung and can increase ventilation perfusion mismatch. The exact mechanisms for meconium-induced inactivation of pulmonary surfactant are not clearly understood. However, several components of meconium, especially fat-soluble (free fatty acids, cholesterol, and triglycerides), and water-soluble (containing bilirubin, bile acids, enzymes, etc.) ones impair lung function [17]. Meconium can impair pulmonary surfactant by a combined action of cholesterol and bile acid present in meconium [18]. Meconium may also change the viscosity and ultrastructure of the surfactant, decrease the levels of surfactant proteins, and also accelerate the conversion from large, surface active aggregates into small, less active forms. The surfactant dysfunction is enhanced by leakage of plasma protein through an injured alveolar-capillary membrane, as well as the proteolytic enzymes, and oxygen-free radical release from activated cells during the inflammation.

Meconium can cause chemical pneumonitis. Meconium is a good chemoattractant for neutrophils [19]. Within a few hours, neutrophils and macrophages are found in the alveoli, larger airways, and lung parenchyma. Meconium is also a source of proinflammatory mediators such as interleukins (IL-1, IL 6, and IL 8), tumor necrosis factors. Thus it may induce inflammation either directly or indirectly through the stimulation of oxidative bursts in neutrophils and alveolar macrophages and may injure the lung parenchyma or lead to vascular leakage causing toxic pneumonitis and hemorrhagic pulmonary edema [2].

Acute intrapulmonary meconium contamination induces a concentration-dependent pulmonary hypertensive response, with 15–20% of infants with the MAS showing PPHN. PPHN in infants with MAS may be caused by (a) pulmonary vasoconstriction secondary to hypoxia, hypercarbia, and acidosis, (b) hypertrophy of the postacinar capillaries as a result of chronic intrauterine hypoxia, and (c) pulmonary vasoconstriction as a result of pulmonary inflammation.

Despite the fact that meconium itself has detrimental effects on placental and umbilical tissues in utero, very little is known regarding the meconium-stimulated cellular and biochemical alterations in fluid-filled fetal lungs [20]. However, heavy meconium staining is supposed to inhibit, through unknown mechanisms, fetal lung fluid reabsorption at birth that may disturb the ability of the lungs to adapt properly to extrauterine life [21].

The extent of lung destruction is not closely correlated to the quantity of meconium in lung tissue but rather to the degree of hypoxia and acidosis present at delivery [22]. Ghidini and Spong postulated that severe MAS may not be in fact causally related to the aspiration of meconium but rather caused by other pathologic processes occurring in utero, such as chronic asphyxia, infection, or persistent pulmonary hypertension [15].

4. Diagnosis of MAS

It is important to monitor infants born through MSAF for any signs of respiratory distress for at least 24 hours. Diagnosis of MAS is based on the presence of respiratory distress in an infant born through MSAF, with no alternate cause for respiratory distress. Chest radiograph and blood gas analysis should be performed if necessary. Because of diverse mechanisms causing this disease, radiographic findings are different. The classic radiographic findings in MAS are overexpansion of the lungs with widespread coarse, patchy infiltrates. However, the severity of the X-ray pattern does not always correlate with the clinical picture. The lack of correlation between clinical severity and radiographic pattern suggests that MAS is less dependent on the amount of meconium obstruction and parenchymal damage than on other aspects of MAS, such as the presence and severity of PPHN.

5. Management of MAS

5.1. Prevention of MAS. The decrease in the incidence of MAS in the last decade has been attributed to the reduction in postterm delivery, aggressive management of abnormal heart rate monitoring, and decreased number of infants with a low Apgar score.

5.1.1. Antepartum Period. Meta-analysis of 14 randomized controlled trials (RCTs) suggests that elective induction of labor for pregnancies at or beyond 41 weeks is associated with significant reduction in the incidence of MAS (RR = 0.43, 95% CI 0.23–0.79) and fewer perinatal deaths (RR = 0.31; 95% CI: 0.11–0.88) compared to expectant management [23].

5.1.2. Intrapartum Fetal Monitoring. Intrapartum monitoring has been recommended to screen for early signs of fetal hypoxia, a risk factor for MAS. There is no evidence that electronic fetal heart rate monitoring (EFM) with or without fetal blood gas and acid-based assessment reduces the risk of fetal or neonatal mortality or morbidity [24]. Fetal scalp pH determination and newer modes like fetal pulse oximetry will improve decision making in timing of delivery and may reduce the incidence of MSAF and MAS [25].

5.1.3. Amnioinfusion. Amnioinfusion has been proposed to reduce the risk of MAS by diluting the meconium, thus reducing its mechanical and inflammatory effects. Amnioinfusion also helps by cushioning the umbilical cord, thus correcting the recurrent umbilical compressions that lead to fetal academia. In a meta-analysis of RCTs, Pierce et al. [26] reported that intrapartum amnioinfusion was significantly associated with reduced risk of MAS (OR 0.30; 95% CI 0.19, 0.46), meconium below the vocal cords, and neonatal acidemia.

In a recent Cochrane meta-analysis of 13 studies, the author stratified the studies based on the clinical settings [27]. Amnioinfusion reduces the risk of MAS only in clinical settings with limited peripartum surveillance (RR 0.25, 95% CI 0.13 to 0.47), but not in clinical settings with standard peripartum surveillance. However, American College of Obstetricians and Gynecologists conclude that routine prophylactic amnioinfusion for the dilution of MSAF is not recommended for the prevention of MAS [28].

5.1.4. Intrapartum Suctioning. In a large multicenter RCT involving 2514 term infants with MSAF comparing intrapartum suction versus no suction, the incidence of MAS (4% versus 4%), mortality, the need of mechanical ventilation, and duration of oxygen therapy were similar in both groups [29]. Therefore, routine intrapartum oropharyngeal and nasopharyngeal suctioning for infants born with clear or meconium-stained amniotic fluid is no longer recommended [30].

5.1.5. Postpartum Endotracheal Suctioning. Neonatal resuscitation program (NRP) recommends intubation and direct endotracheal suction soon after delivery for nonvigorous infants born through MSAF, who have depressed respiratory efforts, poor muscle tone, and/or heart rate less than 100/minute [31]. Cochrane meta-analysis of four randomized studies did not show a difference in the incidence of MAS between intubated and nonintubated vigorous infants [32]. Hence, if the baby born through MSAF has a normal respiratory effort, normal muscle tone, and a heart rate greater than 100 beats per minute, direct endotracheal suction is not recommended. Only suctioning of mouth and nose using a bulb syringe or large bore suction catheter is indicated. According to the International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science, the available evidence does not support or refute the routine endotracheal suctioning of depressed infants born through MSAF [30].

5.2. Treatment of MAS. All infants at risk for MAS who show signs of respiratory distress should be admitted in the neonatal intensive care units. Close monitoring is important since they can deteriorate very quickly. Once the infant develops MAS, management is primarily supportive. Maintenance of optimal thermal environment and minimal handling is essential because these infants are agitated easily, which causes right-to-left shunting, leading to hypoxia and acidosis. Maintenance of adequate oxygenation, optimal blood pressure, correction of acidosis, hypoglycemia and other metabolic disorders is the mainstay of treatment.

5.2.1. Ventilation. Ventilator management of the neonate with MAS is challenging because of the complicated pulmonary pathophysiology resulting from areas of atelectasis and areas of hyperinflation, in association with ventilation-perfusion mismatch and airway compromise [33]. Approximately 40% of babies with MAS require mechanical ventilation and additional 10% require continuous positive airway pressure [34]. There is little evidence from the clinical trials regarding the ventilator treatment of infants with MAS.

Ventilation should be aimed at increasing oxygenation while minimizing the barotrauma that lead to air leak syndromes. The amount of ventilator support depends on severity of respiratory distress. Some infants only require oxygen by hood. In infants with MAS who have hypoxemia (PaO_2 < 50 mm Hg), hypercarbia ($PaCO_2$ > 60 mm Hg), or acidosis (pH less than 7.25) in an oxygen-enriched environment with an inspired oxygen fraction (FiO_2) > 0.6 are often considered candidates for mechanical ventilation.

In infants with MAS without associated PPHN, it is sufficient to maintain a pH of 7.3–7.4, with a PaO_2 targeted between 60 and 80 mmHg and a $PaCO_2$ of 40–50 mmHg. Infants may be started with a moderate peak inspiratory pressure (PIP) preferably not exceeding 25 cm H_2O, a relatively rapid ventilator rate (40–60/min), a moderate positive end expiratory pressure (4–6 cm H_2O), and an adequate expiratory time (0.5–0.7 sec) to prevent gas trapping and air leaks. If gas trapping is noticed, expiratory time may be increased and PEEP should be decreased (3-4 cm H_2O) [33].

In infants with MAS and concomitant PPHN, mild hyperventilation and higher FiO_2 can be considered. But the strategy of achieving hypocapnia and alkalosis by hyperventilation has adverse effects including cerebral vasoconstriction leading to long-term neurologic morbidity as well as air leaks [35, 36]. In such situations other modalities like inhaled nitric oxide and high frequency ventilation should be considered early.

Theoretically High Frequency Ventilation (HFV) minimizes the barotrauma and may reduce air leak syndrome in MAS. No prospective randomized trials have compared conventional ventilation versus HFV in MAS. In pilot studies using inhaled nitric oxide (iNO), Kinsella and Abman [37] found that the combination of HFV and iNO caused the greatest improvement in oxygenation in some patients with severe PPHN. They speculated that improved lung inflation during HFV may augment the response to iNO by decreasing intrapulmonary shunting and improving iNO delivery to the pulmonary circulation [37, 38]. Partial liquid ventilation was found to be a better method of delivering surfactant in an adult rat model of MAS when compared with conventional mechanical ventilation [39]. There is no randomized clinical trial about the use of partial liquid ventilation in human neonates with MAS.

5.2.2. Surfactant Therapy. In vitro studies have shown that meconium interferes with surfactant in several ways: inactivation of its function depending on the concentration, direct toxicity on type II pneumocytes, displacement of surfactant from the alveolar surface, and decrease of surfactant protein A and B levels [2].

Canadian Pediatric Society position statement recommends that intubated infants with MAS requiring more than 50% oxygen should receive exogenous surfactant therapy [40]. Surfactant can be given as either a bolus therapy or bronchoalveolar lavage. Bolus surfactant therapy for MAS has been associated with reduction in the severity of respiratory distress and decrease in the number of infants with progressive respiratory failure requiring ECMO. Meta-analysis of 4 RCTs showed reduction in the severity of respiratory illness and decrease in the number of infants with progressive respiratory failure requiring ECMO (RR 0.64, 95% CI 0.46–0.91) [41]. However, there was no significant difference in mortality, hospital stay, length of ventilation, duration of oxygen use, pneumothorax, pulmonary interstitial emphysema, or chronic lung disease.

Clinical trial of surfactant lavage using Lucinactant in conventionally ventilated infants with MAS found no difference between lavage infants and controls in terms of ECMO requirements, air leak, or duration of ventilation [42]. Similarly, Dargaville and colleagues reported that lung lavage with dilute surfactant (Survanta) in ventilated infants with severe MAS does not decrease the duration of respiratory support, but may produce a reduction in mortality, especially in units not offering ECMO [43].

5.2.3. Role of Steroids. In 2003, Cochrane meta-analysis of two trials [44, 45] including 85 infants with MAS showed that there was no difference in mortality but a small increase in the duration of oxygen treatment in steroid-treated group [46]. Since then, two more trials reported that steroid therapy in MAS was associated with a decrease in the duration of oxygen therapy and hospital stay [47, 48]. The choice of steroid and duration of therapy was different between the studies. Steroids may be beneficial in severe MAS with apparent lung edema, pulmonary vasoconstriction, and inflammation. At present, there is no conclusive evidence to propose routine steroid therapy in the management of MAS. Further research is needed regarding the dosing, timing, and ways of administration of steroids considering their individual properties and possible acute and long-term side effects [49].

5.2.4. Role of Antibiotics. The presence of meconium increases the chances of positive cultures from amniotic fluid in preterm and term infants. However, studies evaluating the development of sepsis in infants with MSAF failed to demonstrate that relationship [50]. Three randomized control studies reported that routine antibiotic prophylaxis is not recommended in the management of MAS for those without perinatal risk factors [51–53]. Antibiotic therapy did not affect the clinical course and outcome related to infection in MAS without perinatal risk factors for infection and without ventilator use. The role of antibiotics in the management of MAS may need to be reevaluated in well-designed trials. Unless there is definite risk for infection, prophylactic use of antibiotics in MAS did not reduce infection. If antibiotics are started for suspected infection due to perinatal risk factors, consider discontinuing antibiotics once the blood culture results are negative.

5.2.5. Nitric Oxide. Severe MAS is often associated with PPHN, resulting in severe hypoxemia. Randomized clinical trials have demonstrated that iNO therapy decreases the need for ECMO in addition to mortality in full-term and near-term neonates with hypoxic respiratory failure and PPHN [54]. For hypoxic respiratory failure due to MAS, infants responded well to combined iNO and HFV as compared to either treatment alone [55]. The response to combined treatment with HFV and iNO reflects both decreased intrapulmonary shunt and augmented nitric oxide delivery to its site of action.

5.2.6. Extracorporeal Membrane Oxygenation. ECMO has been used as a final rescue therapy in infants with severe and refractory hypoxemia associated with MAS. Use of ECMO has been decreased significantly in developed countries with the availability of iNO and HFV. Infants with MAS make up approximately 35% of the infant population who require ECMO [56]. The survival rate has approached 95% of infants with MAS who underwent ECMO [57]. In the ECMO registry, the highest survival rates (>90%) were seen in the patients with MAS who qualified for ECMO [58].

5.2.7. Adjunctive Therapies. All infants with MAS should be monitored using noninvasive monitors (pulse oximeter, transcutaneous O_2/CO_2 methods) and blood gas sampling should preferably be done with an indwelling arterial line. Sedation and analgesia are used frequently in infants with MAS and PPHN to alleviate pain and discomfort that may lead to hypoxia and right-to-left shunting. Opioids, particularly morphine or fentanyl, are frequently used to optimize gas exchange and also to avoid asynchrony, reflex

catecholamine release, and aggravation of pulmonary vascular resistance.

Depolarizing muscle relaxants (pancuronium, vecuronium) were widely used in the past along with opioids to decrease agitation and subsequent hypoxic episodes in ventilated infants. The benefits of neuromuscular blockade include improved oxygenation, decreased oxygen consumption, and decreased accidental extubations. However, the use of neuromuscular blockade remains controversial and is reserved for the infant who cannot be treated with sedatives alone. Neuromuscular blockage can promote atelectasis of dependent lung regions and ventilation perfusion mismatch and may also be associated with increased risk of death [59].

Nearly 30–50% of infants with PPHN do not respond to iNO therapy. Infants who do not show initial response to iNO and those that deteriorate subsequently while on iNO therapy continue to have significant PPHN and need other alternative therapy [60]. Alternatives available include (a) phosphodiesterase-5 inhibitors like Sildenafil, Zaprinast, Milrinone, dipyridamole, (b) prostaglandins like Prostacyclin or PGE1, (c) tolazoline, Magnesium sulfate, (d) NO precursor L-Arginine, (e) free radical scavengers like Superoxide dismutase, (f) experimental agents like Bosentan (endothelin antagonist).

5.2.8. Potential Future Therapy. Currently MAS treatments are all supportive in nature and do not directly affect the injurious actions of meconium on the lung. There is still no effective and safe treatment or prophylactic measure for MAS once the meconium has passed below the vocal cords into the lungs. It has been suggested that fetal pancreatic digestive enzymes play an important role in the lung damage after meconium aspiration by causing disruption of intercellular connections and cell detachment from the basement membrane. A protease inhibitor cocktail prevented the cell detachment induced by meconium suggesting that they may be useful in the treatment and/or prophylaxis [61]. Recent data show that some of the cell death induced by meconium occurs by apoptosis, and therefore has the potential for pharmacologic inhibition through the use of apoptosis blockers or other strategies [62].

6. Conclusions

Despite improvement in obstetrical and neonatal care, MAS continues to be a neonatal disorder with high morbidity and mortality. The lung injury caused by meconium is complex and can be attributed to mechanical obstruction of airways, surfactant inactivation, chemical pneumonitis, and PPHN. Among preventive strategies, elective induction of labor for pregnancies at or beyond 41 weeks is associated with significant reduction in the incidence of MAS and amnioinfusion reduces the risk of MAS only in clinical settings with limited peripartum surveillance. Intrapartum management includes endotracheal suctioning to clear meconium only in nonvigorous infants born through MSAF. The management of a symptomatic infant with MAS is primarily supportive. These infants are at high risk of developing PPHN and air leaks. Invasive ventilation if required should use lower PIP, moderate PEEP, higher rates (40–60/min), and adequate expiratory time and permissive hypercapnea should be tolerated to facilitate gentle ventilation. MAS complicated with PPHN and not responsive to conventional ventilation may require HFV and iNO. iNO therapy has decreased the need for ECMO in MAS complicated by hypoxic respiratory failure and PPHN. Surfactant replacement should be considered in ventilated infants requiring more than 50% FiO_2. Unless there is definite risk for infection, prophylactic use of antibiotics in MAS does not reduce infection or alter the clinical course of illness. ECMO has been used as a final rescue therapy in infants with severe and refractory hypoxemia associated with MAS. The role of steroids and other adjuvant pharmacotherapies like magnesium sulfate, free radical scavengers, and protease inhibitors is still experimental and they are not routinely recommended. As MAS is a major cause of mortality in developing countries, studies focusing on prevention and early treatment should be continued to reduce mortality and morbidity.

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Research Article

A Neonatal Resuscitation Curriculum in Malawi, Africa: Did It Change In-Hospital Mortality?

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Objective. The WHO estimates that 99% of the 3.8 million neonatal deaths occur in developing countries. Neonatal resuscitation training was implemented in Namitete, Malawi. The study's objective was to evaluate the training's impact on hospital staff and neonatal mortality rates. *Study Design*. Pre-/postcurricular surveys of trainee attitude, knowledge, and skills were analyzed. An observational, longitudinal study of secondary data assessed neonatal mortality. *Result*. All trainees' ($n = 18$) outcomes improved, ($P = 0.02$). Neonatal mortality did not change. There were 3449 births preintervention, 3515 postintervention. Neonatal mortality was 20.9 deaths per 1000 live births preintervention and 21.9/1000 postintervention, ($P = 0.86$). *Conclusion*. Short-term pre-/postintervention evaluations frequently reveal positive results, as ours did. Short-term pre- and postintervention evaluations should be interpreted cautiously. Whenever possible, clinical outcomes such as in-hospital mortality should be additionally assessed. More rigorous evaluation strategies should be applied to training programs requiring longitudinal relationships with international community partners.

1. Introduction

There are 3.82 million neonatal deaths each year with a global neonatal mortality rate of 30 per 1000 live births [1]. The World Health Organization (WHO) estimates that each year 99% of those neonatal deaths occur in developing countries [2]. Neonatal mortality from birth asphyxia ranges from 40 to 610 neonatal deaths per 1000 live births [3–5], and nearly 1 out of every 4 neonatal deaths in Malawi is a result of birth asphyxia [6]. A lack of protocol and systemized training in neonatal resuscitation to reduce neonatal mortality secondary to birth asphyxia is common across sub-Saharan Africa [7]. As such, the United Nations' Millennium Development Goal 4—to reduce the 1990 mortality rate among under-five children by two-thirds by 2015—cannot be realized without educational efforts in neonatal resuscitation. As neonatal deaths make up 41% of under-5 mortality [8], neonatal resuscitation training is key.

Effective neonatal resuscitation is possible with basic equipment and skills in low-resource settings [9]. Case studies from China and India reveal that 90% of newborns with asphyxia require only drying, warming, and stimulation for complete revival [10, 11]. Such techniques coupled with ensuring a patent airway, suctioning, ventilation, administering oxygen, and chest compressions are part of the Neonatal Resuscitation Program (NRP) [12], an educational intervention based on the consensus of science and resuscitation guidelines of the International Liaison Committee on Resuscitation and published by the American Academy of Pediatrics and the American Heart Association. NRP is the developed world's standard of care to prevent death and complications of cerebral palsy due to asphyxia [13], and, when systematically implemented by trained personnel, has the potential to annually prevent 192 000 intrapartum-related neonatal deaths worldwide and 5–10% of deaths related to preterm complications [14]. Curriculums with components of NRP have significantly improved healthcare

providers' knowledge, skills, and attitudes in developing countries [15, 16] and decreased neonatal mortality in the developing world up to 65.7 percent [10, 17, 18]. One study revealed declines in national trends of neonatal mortality over an 8-year period following NRP integration across Malaysia [19]. Furthermore, a 44.6% decline in neonatal mortality was seen with WHO's Essential Newborn Care (ENC) curriculum in Zambia, a resuscitation curriculum separate from the NRP [20]. Conversely, a recent study of ENC among 57 643 infants and NRP among 62 366 infants showed no reduction in mortality rates for either program [21]. Resource-constricted environments, often overflowing with competing needs and challenges like staff turnover, outdated equipment, and low levels of education, can render true change challenging to accomplish. Because the literature reports conflicting results following NRP training, a meta-analysis was performed which was inconclusive on all-cause neonatal mortality [22].

An increasing number of medical students and residents spend professional time working abroad [23, 24]. International health experiences have been shown to increase students' interest in public health, likelihood of choosing a career in primary care, and commitment to serving the underserved [25]. Many medical schools and residency programs now offer global health curriculum tracks, elective clinical rotations, and opportunities for research in developing world settings. Unfortunately, such research tends to examine short-term programs using pre- versus postintervention evaluations of participants while failing to evaluate patient outcomes. This reality is reflected in the current literature surrounding the assessment of neonatal resuscitation training efforts in the developing world [26–29].

Pediatric residents at Stanford University's Lucile Packard Children's Hospital (LPCH) developed a partnership with St. Gabriel's Hospital in Namitete, Malawi, Africa in January 2008. Stanford residents conducted a needs assessment in March 2008 that identified an interest in neonatal resuscitation training for the hospital's staff to reduce neonatal mortality. In response, Stanford residents developed and implemented NRP-based training to train St. Gabriel's Hospital physicians, clinical officers, and midwives ($n = 14$). The goal of this project was to evaluate the intervention on two levels: (1) the impact on trainees through a pre-/postcurricular evaluation and (2) the impact on neonatal mortality rates at St. Gabriel's Hospital.

2. Methods

2.1. Neonatal Resuscitation Training

2.1.1. Intervention. The curriculum was based upon the American Academy of Pediatrics NRP [12] and tailored in response to the constricted time and resources deemed feasible by on-site community leaders. The curriculum required a total of 6 hours: two hours of lecture, one hour of demonstration, and three hours of hands-on, scenario-driven sessions using mannequins to address components of NRP techniques, and oxygen was available (Table 1). During September of 2008, weekly training sessions for small groups of employees ($n =$ 4-5) were held. The course was taught on one day by two Pediatrics residents in the same room with all 14 participants present.

2.1.2. Evaluation. A survey tool was developed to assess pre-/posteducational intervention impact. The survey consisted of 18 queries covering three domains: attitude, knowledge, and skills. This tool was developed with the assistance of an expert in survey design, pilot-tested, and modified accordingly. Students' t-test was used to compare mean score changes for the pre-/post-educational intervention surveys. The pre-/postintervention instrument can be obtained by contacting the lead author.

2.2. Neonatal Mortality

2.2.1. Design. An observational, longitudinal study, and secondary data analysis was performed by data abstraction from existing hospital administration data provided by St. Gabriel's Hospital. Total neonatal deaths was the primary outcome for this analysis. Retrospective data revealed 20.9 neonatal deaths per 1000 live births at St. Gabriel's Hospital. Assuming a 44.6% decline [10, 17, 18, 20] to 11.6 neonatal deaths per 1000 live births, a two-tail test with 80% statistical power and a 95% confidence interval required at least 2956 subjects in both arms.

2.2.2. Data Source. Health Facility Surveillance Forms (HFSFs), collected since 1971, contained anonymous data transferred from admission, delivery, and female ward books by a St. Gabriel's Hospital Records Assistant. The HFSFs included total number of deliveries, neonatal and maternal complications, and live births reported for each calendar month. The neonatal complications recorded included 5-minute Apgar 5 or less/asphyxia, neonatal sepsis, born-before-arrival, premature baby, baby less than 2500 grams, malformation, and HIV-infected. Maternal complications included prolonged obstructed labor, antepartum hemorrhage, postpartum hemorrhage, severe preeclampsia, eclampsia, puerperal sepsis, ruptured uterus, retained placenta, ectopic pregnancy, abortion, and anemia. Data for stillbirths were incomplete and thus unable to be analyzed. Birth datasets from 2006 to 2008 at St. Gabriel's Hospital showed approximately 3000 live births during any 15-month period. Thus, datasets for 15 months (June 2007 to August 2008) before intervention and 15 months (October 2008 to December 2009) after intervention were analyzed. Datasets from September 2008, the month of neonatal resuscitation training, were excluded.

2.2.3. Statistical Analysis. Contingency tables of neonatal mortality and survival and a Fisher's Exact Test were calculated to compare the proportion of neonatal mortality prior to and following the LPCH NPR curriculum intervention. The evaluation was based on total number of deaths during the two 15-month periods. A P value of less than 0.05 was considered statistically significant. SPSS version 17.0 software was used. The Stanford University Institutional Review Board determined that this study does not meet the

Table 1: LPCH neonatal resuscitation program curriculum[1].

Hour	Method of instruction	Session content
1	Lecture	(i) Neonatal resuscitation curriculum overview and need (ii) Fetal circulation and oxygenation (iii) Fetal complications after labor (iv) Signs of compromised infant (v) Supplies needed for neonatal resuscitation (vi) Determination of need for resuscitation (vii) Initial assessment (a) Term (b) Amniotic fluid (c) Respirations (d) Tone (viii) Initial steps (a) Warming technique (b) Drying technique (c) Infant positioning to open airway (d) Clear airway (e) Stimulation technique (ix) Infant vitals (a) Respirations (b) Heart Rate (c) Color (x) Advanced techniques (a) Positive pressure ventilation (b) Chest compressions (xi) NRP-based special considerations adapted to local context
2-3	Demonstration with trainee practice and instructor feedback[2]	(i) Warming technique (ii) Drying technique (iii) Infant positioning for open airway (iv) Suctioning techniques (a) Oral (b) Nasal (c) Deep (v) Stimulation technique (vi) Bag-valve-mask technique (vii) Chest compression technique
4	Scenarios[3]	(i) Unexpected depressed infant (ii) Maternal preterm delivery and hemorrhage (iii) Hypothermia (iv) Meconium (v) Depressed infant due to sedation
5-6	Lecture	(i) Review (ii) Question and Answer Session

[1] NRP has 7 lessons: (1) Principles of Resuscitation, (2) Initial Steps in Resuscitation, (3) Bag and Mask Ventilation, (4) Chest Compression, (5) Endotracheal Intubation, (6) Medications, and (7) Special Considerations. The LPCH NRP-based curriculum incorporates lessons (1), (2), (3), (4), and (7).
[2] Infant mannequins are used for demonstrations and trainee practice sessions.
[3] NRP scenarios are adapted to local context and read by course instructor. Trainees react to the scenario while practicing resuscitation skills on infant mannequins. Instructor provides feedback as necessary on sequential steps of proper neonatal resuscitation for each scenario.

Table 2: Changes in trainees' attitude, knowledge, and skills in neonatal resuscitation.

Domain	Mean preintervention score (percent correct)	Mean postintervention score[1] (percent correct)
Attitude Example: "*How comfortable are you with neonatal resuscitation?*" Likert scale, 1–4, Not at all to very comfortable, scored on quartiles: 1 = 25%, 2 = 50%, 3 = 75%, 4 = 100%	45	76
Knowledge Example: "*Restoration of adequate ventilation usually will result in a (rapid) (gradual) (slow) improvement in heart rate.*" Dichotomous correct or incorrect answer scored.	30	59
Skills Example: "*Please demonstrate the proper method of positive-pressure ventilation.*" Dichotomous correct or incorrect answer scored.	58	76

[1] Combined Students' paired t-Test with two-tailed distribution, ($P = .02$).

Table 3: Birth outcomes at St. Gabriel's Hospital before and after LPCH neonatal resuscitation training.

	Preintervention	Postintervention
Total deliveries	3449	3515
Total neonatal deaths	72	77
Total maternal deaths	14	7
Neonatal mortality	20.876 per 1000	21.906 per 1000
Maternal mortality	4.059 per 1000	1.991 per 1000
5-minute Apgar score less than 5	131	66

Fisher's exact test indicates that the difference between pre- and postintervention percent neonatal mortality is not statistically significant, ($P = 0.86$). The difference between pre- and postintervention percent maternal mortality is not statistically significant, ($P = 0.24$).

Human Research Protection Program's definitions of human subject research because we did not obtain or receive private, individually identifiable information.

3. Results

Fourteen of 26 birth attendants at St. Gabriel's received training at St. Gabriel's Hospital in September 2008. The trainees consisted of two physicians, eight clinical officers, and four midwives. No trainees had previous neonatal resuscitation training and all trainees worked in the labor ward, antenatal unit, and female ward from October 2008 to December 2009. One trainee was further trained as an instructor. The pre-/posttest comparison evaluating all aspects of the module found that training scores improved from an average of 38.6% to 64.4%: attitude scores improved from 45% to 76.3%, knowledge scores improved from 30.4% to 58.7%, and skills scores improved from 57.5% to 75.5%, ($P = .02$) (Table 2).

A total of 6 694 neonates born at St. Gabriel's Hospital were studied. There were 3 449 births preintervention and 3 515 births postintervention (Table 3, see the appendix). The neonatal mortality rate across the study's first 15 months (before intervention) was 20.9 neonatal deaths per 1000 live births compared to 21.9 neonatal deaths per 1000 live births in the 15 months after intervention, a 0.10% difference, ($P = 0.86$) (Table 3). The five-minute Apgar score less than 5 fell from 131 preintervention to 66 postintervention (Table 3). Complete data on neonatal deaths (to 28 days) was not available; only in-hospital deaths are recorded. Maternal mortality was 4.1 maternal deaths per 1000 live births preintervention compared to 2.0 maternal deaths per 1000 live births postintervention, ($P = 0.24$) (Table 3).

4. Discussion

The results of our study reject the hypothesis that neonatal mortality rates are lower at St. Gabriel's Hospital following the LPCH neonatal resuscitation curriculum intervention, despite the positive results of the pre-/postintervention evaluation. This highlights the necessity for evaluating interventions at the level of the primary outcome—in this case, neonatal mortality—and not relying on intermediary results like trainee attitude, knowledge, and skills. While the neonatal mortality rates before the LPCH neonatal resuscitation curriculum (20.9 neonatal deaths per 1000 live births) and after the intervention (21.9 per 1000) were not statistically different, it is interesting to note that the neonatal complication of a five-minute Apgar score less than 5 was decreased postintervention. It is possible that the LPCH neonatal resuscitation training had a positive impact for a small group of health providers reflected by the reduction of the five-minute Apgar score less than 5 from 131 preintervention to 66 postintervention. However, it appears

that the clinical impact was not sufficient to reduce overall in-hospital mortality.

There are four possible explanations for the discordant results between our pre-/postintervention evaluation data and our mortality data. First, the modification of NRP required for the program's effectiveness within this time- and resource-deprived setting may have resulted in the unchanged rates of neonatal mortality. The modifications may have rendered the curriculum too short. What may be efficacious in a controlled setting might not be feasible or effective in developing communities. Second, factors external to the curriculum may have overwhelmed any statistically significant impact. For example, there was staff turnover with seven of the 14 health workers who received the LPCH neonatal resuscitation training continuing to work at St. Gabriel's. This likely had a negative impact on the level of neonatal resuscitation at deliveries. This creates a compelling case for the necessity of longitudinal train-the-trainer programs for St. Gabriel's staff. Third, our curriculum may not have addressed crucial aspects in the care of neonates. For example, the WHO Essential Newborn Care program addressed topics like cleanliness, temperature management, infection prevention, skin-to-skin care, breastfeeding, care of the small infant, and care of common illnesses. A recent study shows this program's relative effectiveness in reducing neonatal mortality rates [30]. Fourth, the LPCH neonatal resuscitation curriculum may not incorporate enough adult learning theory. Simulation-based training can be an effective educational methodology to promote skill acquisition and performance enhancement in neonatal resuscitation providers [31]. The LPCH neonatal resuscitation curriculum may be overwhelmed by didactical instruction (representing three of the six total hours) compared to hands-on activity. We hope that a qualitative assessment of the LPCH neonatal resuscitation training at St. Gabriel's Hospital will allow our community partner to make recommendations for further curriculum modifications.

Our findings are consistent with a study in Zambia that reports significant improvement in healthcare providers' knowledge and skills following curriculum intervention despite a limited application of curriculum guidelines due to local conditions [16]. Although NRP training reduces neonatal mortality in controlled, nonrandomized studies in China, India, and Africa [10, 15, 32, 33], the literature surrounding NRP curriculums' impact is not consistent. Our results contribute to that literature. These findings may have important implications for the children of the developing world born without adequate neonatal resuscitation services because of the complexity and high program cost [13, 34]. However, if 90% of asphyxiated newborns require only drying, warming, and stimulation for survival, then an abbreviated NRP-based curriculum could improve outcomes in an affordable way [10].

There has been a general progression in the evidence behind neonatal resuscitation. The WHO published its abbreviated NRP called Basic Newborn Resuscitation (BNR) in 1997 [35], a potential outline for future programs aimed at reducing developing world neonatal mortality. The assessment of BNR's effect on outcomes has been limited. It is possible that, like the LPCH neonatal resuscitation curriculum, such abbreviated education programs may not improve outcomes and be too costly in time. Health care workers' time away from patient care while in workshops can be a difficult obstacle to overcome, particularly in the developing world. However, Helping Babies Breath (HBB) [36], an evidence-based educational program released in June 2010 by the American Academy of Pediatrics, was developed to improve and be compatible with existing neonatal resuscitation programs experiencing the common obstacles of low-resource settings. HBB trains birth attendants in only the essential skills of newborn resuscitation (assessment, temperature support, stimulation to breathe, and assisted ventilation as needed) with particular emphasis on the first minute after birth. Studies to assess HBB's impact on outcomes are underway.

Our study has five important limitations to consider. First, its retrospective analysis of large aggregate data brings inherent restrictions. Data at the individual patient level could have revealed a statistically significant impact of the LPCH neonatal resuscitation curriculum on neonatal mortality for certain subpopulations of neonates born at St. Gabriel's such as stillbirths. A prospective study, for example, in India found that while neonatal mortality did not decrease following the implementation of neonatal resuscitation programs, asphyxia-related deaths did significantly decline [33]. We were limited in our ability to individually track cases because such data is not collected at St. Gabriel's Hospital; thus, we were unable to compare the two cohorts on variables such as maternal age, prenatal health, and maternal health. Efforts to collect this individual patient data pose a significant administrative burden to our community partner. Second, the nature of the busy labor wards at St. Gabriel's Hospital poses a significant challenge to collecting data on how many deliveries are covered by individuals who received LPCH neonatal resuscitation training and if the skills learned during training are applied in postintervention months by trainees. Third, our results may be limited in generality. This was a unique NRP-based curriculum in a specific developing community. However, curricula must be tailored to meet the needs and realities of their settings. Fourth, we may have experienced a glass-ceiling effect. The Malawian neonatal mortality rate is low as compared to much of the developing world as it falls below the 30 deaths per 1000 live births target of Millennium Development Goal number 4 [6]. Finally, we were unable to compare the pre- and postintervention maternal complications given that the data were collected in aggregate. It was impossible to determine whether the observations were independent of one another as one female might have given birth during both the pre- and postintervention periods. Analytical approaches were limited due to the two samples violating the assumption of independence.

5. Conclusion

Global health interventions require robust evaluation. Short-term pre- versus postintervention assessments frequently show positive results, as ours did. These results are only

Table 4: Pre- versus postintervention neonatal mortality rate.

Time	Live births	Total neonatal deaths	Total deliveries	Percent mortality
June 2007	241	1	242	0.004132
July 2007	208	6	214	0.028037
August 2007	279	8	287	0.027875
September 2007	285	7	292	0.023973
October 2007	267	4	271	0.014760
November 2007	175	1	176	0.005682
December 2007	198	3	201	0.014925
January 2008	208	9	217	0.041475
February 2008	172	3	175	0.017143
March 2008	203	4	207	0.019324
April 2008	200	3	203	0.014778
May 2008	205	7	212	0.033019
June 2008	217	6	223	0.026906
July 2008	245	6	251	0.023904
August 2008	274	4	278	0.014388
Total preintervention	3377	72	3449	0.020876
October 2008	280	6	286	0.020979
November 2008	217	1	218	0.004587
December 2008	259	6	265	0.022642
January 2009	193	4	197	0.020305
February 2009	207	1	208	0.004808
March 2009	224	2	226	0.008850
April 2009	177	2	179	0.011173
May 2009	213	4	217	0.018433
June 2009	227	10	237	0.042194
July 2009	263	9	272	0.033088
August 2009	260	15	275	0.054545
September 2009	266	4	270	0.014815
October 2009	191	4	195	0.020513
November 2009	227	9	236	0.038136
December 2009	234	0	234	0.000000
Total postintervention	3439	77	3515	0.021906

proximal measures, however, and do not evaluate many projects' goals such as reducing neonatal mortality. We believe the primary contribution of this study is that it creates a compelling case for applying rigorous evaluation strategies to international health education initiatives. Longitudinal relationships with community partners are required for thorough evaluation. Short-term commitments can be unhelpful, costly in time and money, or even harmful. We aspire to practice evidence-based medicine for the betterment of patient outcomes as physicians in the United States. We should hold ourselves to the same, high standards when providing care to the developing world.

Appendix

For more details, see Table 4.

Abbreviations

BNR: Basic newborn resuscitation
ENC: Essential newborn care
HFSFs: Health facility surveillance forms
HBB: Helping babies breathe
LPCH: Lucile Packard Children's Hospital
NRP: Neonatal Resuscitation Program
WHO: World Health Organization.

Conflict of Interests

The authors declare no conflict of interests.

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Review Article

Postnatal Corticosteroids for Prevention and Treatment of Chronic Lung Disease in the Preterm Newborn

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Despite significant progress in the treatment of preterm neonates, bronchopulmonary dysplasia (BPD) continues to be a major cause of neonatal morbidity. Affected infants suffered from long-term pulmonary and nonpulmonary sequel. The pulmonary sequels include reactive airway disease and asthma during childhood and adolescence. Nonpulmonary sequels include poor coordination and muscle tone, difficulty in walking, vision and hearing problems, delayed cognitive development, and poor academic achievement. As inflammation seems to be a primary mediator of injury in pathogenesis of BPD, role of steroids as antiinflammatory agent has been extensively studied and proven to be efficacious in management. However, evidence is insufficient to make a recommendation regarding other glucocorticoid doses and preparations. Numerous studies have been performed to investigate the effects of steroid. The purpose of this paper is to evaluate these studies in order to elucidate the beneficial and harmful effects of steroid on the prevention and treatment of BPD.

1. Introduction

Despite significant progress in the treatment of preterm neonates, bronchopulmonary dysplasia (BPD) continues to be a major cause of neonatal morbidity. At earlier times, it was considered to be primarily iatrogenic in etiology as a consequence of crude ventilator techniques. In current time with advanced and sophisticated ventilator techniques, BPD continued to be a major sequel of neonatal respiratory distress syndrome (RDS), primarily because of better survival of extreme premature babies with other factors including ventilator-induced lung injury, exposure to oxygen, and inflammation. New bronchopulmonary dysplasia (new BPD) is characterized, in part, by arrested alveolar and vascular development of the immature lung [1]. Affected infants suffer from long-term pulmonary and nonpulmonary sequel. The pulmonary sequels include reactive airway disease and asthma during childhood and adolescence [2, 3]. Nonpulmonary long-term sequels include poor coordination and muscle tone, difficulty in walking, vision and hearing problems, delayed cognitive development, and poor academic achievement [4].

The proposed etiology of new BPD is the initiation of inflammatory mediators that cause impairment of alveolarization and vasculogenesis [5]. The lacking anti-inflammatory mediators in the preterm neonate may be inundated easily by the proinflammatory cascade. A difference in the release of pro- and anti-inflammatory cytokines, occurring as a result of intrauterine/postnatal infection (sepsis), ventilator trauma, oxidants, pulmonary edema, or sepsis, damages the immature lung.

As inflammation seems to be primary mediator of injury in pathogenesis of BPD, role of steroids as anti-inflammatory agent has been extensively studied and proven to be efficacious in management. But studies in last one and half decade have seriously questioned the routine use

of steroids especially high-dose dexamethasone due to its long-term effect on neurodevelopment. In 2010, the American Academy of Pediatrics (AAP) revised policy statement regarding the use of postnatal corticosteroids for prevention or treatment of chronic lung disease in preterm infants, concluded that high-dose dexamethasone (0.5 mg/kg/day) does not seem to confer additional therapeutic benefit over lower doses, and is not recommended. Evidence is insufficient to make a recommendation regarding other glucocorticoid doses and preparations. The clinician must use clinical judgment when attempting to balance the potential adverse effects of glucocorticoid treatment with those of BPD. Postnatal use of dexamethasone for BPD has decreased since the publication of the AAP statement in 2002; however, the incidence of BPD has not decreased [6]. Instead, several reports have suggested that the incidence or severity of BPD may have increased. Despite AAP statement to limit the use of systemic dexamethasone especially high dose, seems reasonable considering it has proven adverse effect on neurodevelopment. But that cannot negate the fact that steroids do have beneficial effects on pulmonary physiology, and currently we do not have any other anti-inflammatory of similar efficacy. If we can limit the systemic side effects of steroid in some way and can utilize its local anti-inflammatory effect on lung, it can be a very useful drug in management of new BPD.

Various mechanisms have been described for beneficial effect of steroids on lung mechanics in infants with BPD. Various steroids of different potency have been studied at various timings; in different dosing regimens; for different duration; in different forms (including intravenous, inhalational, intratracheal, and recently intratracheal with surfactant as a vehicle). Amongst systemically used steroids, dexamethasone comes as the most potent and most studied one. It has been studied in early (<7 days), moderately early (7–14 days) and late/delayed (>14 days), postnatal periods and dosing ranging from 0.1 mg/kg/day to 0.5 mg/kg/day and duration ranging from 3 days to 42 days. Hydrocortisone comes second. Beclomethasone is the most commonly used inhalational steroid for BPD. Recently, budesonide has been tried as intratracheal instillation with or without surfactant as a vehicle and shown to reduce inflammatory marker in tracheal aspirates in initial clinical trials.

2. Possible Mechanisms of Action of Glucocorticoids

As the pathogenesis of BPD is multifactorial, so are the mechanisms to respond to steroid therapy. Since inflammation seems to play a critical role in the evolution of BPD, benefit seen with glucocorticoids most likely mediates through its anti-inflammatory effect.

The primary anti-inflammatory effect of glucocorticoids is mediated by annexin-1 synthesis. Annexin-1 suppresses phospholipase A2 expression, thereby blocking eicosanoids (i.e., prostaglandins, thromboxanes, prostacyclins, and leukotrienes) and the subsequent leukocyte inflammatory events including adhesion and migration. Thus, glucocorticoids inhibit two main products of inflammation prostaglandins and leukotrienes. In addition, glucocorticoids also suppress both cyclooxygenase I and II similar to NSAID, potentiating the anti-inflammatory effect [7].

Lung inflammation is downregulated by dexamethasone therapy. Groneck et al. evaluated the tracheobronchial aspirate from preterm infants at high risk of BPD. The number of neutrophils and concentrations of leukotriene B4, interleukin-1, elastase-α1-protease inhibitor, and albumin were decreased after dexamethasone treatment [8]. It indicates that dexamethasone affects the release of inflammatory mediators and neutrophils influx into the airways of preterm infants who require mechanical ventilation and decreases the microvascular permeability. Pulmonary edema is the hallmark of BPD; dexamethasone has been shown to reduce the pulmonary edema in infants with BPD.

Glucocorticoids block the release of arachidonic acids and its subsequent conversion to eicosanoids. The decreased incidence of patent ductus arteriosus (PDA) after prenatal or postnatal steroid therapy is likely due to the influence of the corticosteroid effect on the responsiveness of ductal tissue to prostaglandins. Prostaglandin has an important role in maintaining the integrity of gastrointestinal mucosa. The use of steroids may increase the risk of gastrointestinal perforation. Other mechanisms such as modulating the transcription and posttranscriptional regulation of surfactant component, stimulation of antioxidant production, and enhancement of adrenergic activities may also be responsible for the acute and rapid improvement of pulmonary function [9]. Unfortunately, some of these mechanisms are also involved in physiologic signaling other than inflammatory signaling; the therapeutic effects of glucocorticoids in inflammation are often accompanied by clinically significant side effects. Glucocorticoid receptors are present virtually in all cells. Prolonged or high-dose glucocorticoids therapy causes multiple systemic side effects. There is a consensus that the desired anti-inflammatory effects of glucocorticoids are mainly mediated via repression of gene transcription. In contrast, the underlying molecular mechanisms for glucocorticoids-mediated side effects are complex and partly understood.

3. Postnatal Corticosteroid Therapy in Preterm Infants

3.1. Choice of Glucocorticoids. Dexamethasone is a potent, long-acting steroid with exclusive glucocorticoid effect. When compared to hydrocortisone, dexamethasone is 25–50 times more potent. The half-life is 36–54 hours. Dexamethasone has been extensively studied in neonatal medicine and has shown to improve pulmonary function, facilitate extubation, and decrease the incidence of BPD [10–15]. However, many associated adverse side effects prevent the routine use of dexamethasone. The short-term side effects include hyperglycemia, hypertension, hypertrophic cardiomyopathy, gastrointestinal bleeding, and perforation. The risk

of gastrointestinal perforation increases with concomitant indomethacin treatment [16]. There is also a concern with the chronic suppression of the hypothalamic-pituitary-adrenal axis [17, 18] and long-term neurodevelopmental delay [19, 20].

On the other hand, hydrocortisone has almost equal glucocorticoid and mineralocorticoid action, and the half-life is only 8 hours. Sick premature infants have relative adrenal insufficiency during acute illness because of developmental immaturity of the hypothalamic-pituitary-adrenal axis suggesting that an early physiological replacement of cortisol may be needed [21–24]. However, large doses above physiologic levels to achieve the anti-inflammatory action may cause significant mineralocorticoid side effects. Early use of hydrocortisone (<48 hours) was shown to decrease the risk of PDA but increased survival only in infants exposed to maternal chorioamnionitis or who had low cortisol values [22, 23].

Another steroid betamethasone, a stereoisomer of dexamethasone, differs only in the orientation of the methyl group at position 16. However, this structural difference could be responsible for marked differences in nongenomic effects. Previous antenatal steroid studies have demonstrated that both drugs have the same effects in reducing the risk of intraventricular hemorrhage, but betamethasone has been shown to be more effective than dexamethasone in reducing the risk of neonatal death and cystic periventricular leukomalacia among very premature infants [24, 32]. The study of betamethasone in postnatal use is limited. A recent study has shown that betamethasone is as effective as dexamethasone in improving pulmonary function, but with fewer adverse effects, such as poor weight gain and hyperglycemia [33].

Inhaled glucocorticoids have been used in neonates without concomitant systemic side effects. They have been successfully used for years in asthmatic patients, but their effects on mechanical ventilated preterm infants are less impressive. The delivery of inhaled glucocorticoids in preterm infants is technically difficult, and its effectiveness has been shown to be limited. Similarly, direct intratracheal instillation of glucocorticoids alone has also not been shown to be effective. A topical glucocorticoid aerosol (budesonide, fluticasone, or beclomethasone) is administered by metered dose inhaler and spacer directly to the endotracheal tube of intubated infants. In an animal model, delivery of beclomethasone to the lungs of an intubated neonate was only 1-2% of the original aerosolized drug [34]. The inhaled steroid did not decrease the incidence of BPD but improved blood gas, chest X-ray score, and a decrease in the use of systemic steroids [35–38].

A recent study from Yeh et al. suggested that intratracheal instillation of budesonide, a strong local glucocorticoids, using surfactant as vehicle may effectively deliver the medication to the lung and may decrease the incidence of BPD [39].

3.2. Timing of Postnatal Steroid Use. The potential mechanism of glucocorticoids in premature infants with RDS is not exactly known. Most of the clinical trials only evaluated clinical responses and did not study mechanisms explaining the beneficial effects. Based on the pathologic and physiologic studies, it seems that steroid therapy given at different times may mediate physiologic effect via different mechanisms. Premature infants may develop lung injury shortly after birth and during the first 1-2 weeks after exposure to infection, oxygen, or positive pressure ventilation. Therefore, steroid should be given shortly after birth or during the first few weeks to prevent BPD via its anti-inflammatory action. On the other hand, steroid therapy given at 3–6 weeks of life may derive its benefits from the modulation of lung repair. Alternately, steroids given at any age may be effective in infants with BPD by blunting hyperreactivity and inflammation.

3.3. Dosage and Duration of Corticosteroids. Most recent studies used a dose of dexamethasone 0.1–0.5 mg/kg/day, equivalent to 10 to 20 times of endogenous corticosteroid levels, in durations ranging from 3 to 42 days. The high dosage and long duration of treatment might be responsible for the delay of brain growth and subsequent poor neurodevelopmental outcomes. A lower dose and shorter duration of dexamethasone may be beneficial and without significant side effects. However, the proper dosage and duration of treatment has not been well defined.

Compare to dexamethasone, the dosage of hydrocortisone used in the trials aimed to prevent BPD was smaller, ranging from 1-2 mg/kg/day, which is equivalent to 1 to 2 times the physiological level. Unfortunately, the low-dose replacement showed no reduction of BPD.

4. Current Evidence of Steroid Use: AAP Revised Policy, 2010

4.1. Dexamethasone. Current evidence suggests that dexamethasone may decrease mortality rates, facilitate extubation, and generally decrease the incidence of BPD but that it carries a significant risk for short- and long-term adverse effects, especially impairment of growth and neurodevelopment [6, 53–56].

(1) Cochrane database systemic review concluded that the benefits of dexamethasone therapy in the first week of life may not outweigh its many adverse effects [57]. In contrast, it concludes that treatment after the first postnatal week may reduce mortality rates without increasing adverse long-term neurodevelopmental outcomes although long-term follow-up data remain limited [58].

(2) Two other systemic meta-analyses have been done recently. In the first review, a risk-weighted meta-analysis, the authors emphasized the importance of the a priori risk of death or BPD in different study populations [59]. In this analysis, the incidence of death or cerebral palsy (CP) was increased among dexamethasone-treated infants compared with placebo-treated infants in studies that enrolled patients at low risk (<35%) of BPD. In contrast,

Table 1: RCTs of dexamethasone to prevent or treat BPD reported since 2001.

Study, no. of centers	*n*	Eligibility criteria (all on mechanical ventilation)	Timing	Dexamethasone dosing regimen	Outcome
McEvoy et al. [25], 1 center	62	500–1500 g BW; ≤32 wk gestation	7–21 postnatal days	5 mg/kg/day tapered over 7 days versus 0.2 mg/kg tapered over 7 days	Rate of survival without BPD 76% versus 73% (NS); no benefit to higher dose
Odd et al. [26], 1 center	33	≤1250 g BW	1–3 wk of age	0.5 mg/kg/day tapered over 42 days versus "individualize" (same dose, shorter course)	Rate of survival without BPD: 24% versus 30% (NS); no difference in 18-month outcomes
Malloy et al. [27], 1 center	16	<1501 g BW; <34 wk gestation	<28 postnatal days	0.5 mg/kg/day tapered over 7 days versus 0.08 mg/kg/day for 7 days	Rate of survival without BPD: 11% versus 38% (NS); higher dose had more adverse effects, no apparent benefit
Walther et al. [28], 1 center	36	≥600 g BW; 24–32 wk gestation	7–14 d postnatal age	0.2 mg/kg/day tapered over 14 days versus placebo	Rate of survival without BPD: 65% versus 47% (NS); extubation: 76% versus 42% ($P < .05$)
Anttila et al. [29], 6 centers	109	500–999 g BW; ≤31 wk gestation	Eligible at 4 h of age	0.25 mg/kg every 12 h × 4 doses versus placebo	Rate of survival without BPD: 58% versus 52% (NS)
Doyle et al. [30], 11 centers	70	<1000 g BW; <28 wk gestation	>1 wk postnatal age	0.25 mg/kg every 12 h × 4 doses versus placebo	Rate of survival without BPD: 14% versus 9% (NS); extubation: 60% versus 12% (odds ratio: 11.2 (95% confidence interval: 3.2–39.0))
Rozycki et al. [31], 1 center	61	650–2000 g BW	≥14 day postnatal age	0.5 mg/kg/day tapered over 42 day versus inhaled beclomethasone at 3 different doses for 7 days followed by the above-listed dexamethasone course, if still mechanically ventilated	Rate of survival without BPD: 53% versus 46% (NS); extubation by 7 d: 7 of 15 versus 6 of 46 ($P < .01$)

BW = body weight; NS = not significant.

dexamethasone treatment decreased the risk of death or CP when infants at high risk of BPD (≥65%) were studied [59]. Thus, for infants at the highest risk of BPD, the beneficial effect of dexamethasone in reducing lung disease seemed to outweigh its adverse effect of increasing the risk of CP. In the second meta-analysis, the authors compared outcomes for trials with different cumulative doses of dexamethasone and concluded that a higher cumulative dose improved rates of survival without BPD and did not increase adverse long-term effects [60].

(3) Small individual randomized controlled trials (RCTs) that directly compared high-versus low-dexamethasone doses, variably defined, have revealed no differences in efficacy (Table 1) [25–27]. These studies have generally been small and heterogeneous, which makes them difficult to compare.

(4) Three RCTs have compared dexamethasone to placebo (Table 1); 1 was small and the other 2 were stopped early and are, therefore, underpowered [28–30]. One trial compared an early, short course of dexamethasone to placebo and revealed no significant difference in mortality or BPD rates [29]. The other 2 trials evaluated the efficacy of a later, lower-dose course of dexamethasone for facilitating extubation, and the authors reported that significantly more dexamethasone-treated infants were successfully extubated during the treatment period [28, 30]. Similar results were reported from an additional study that compared systemic dexamethasone to inhaled beclomethasone for extubation; significantly more dexamethasone-treated infants were successfully extubated within 7 days (Table 1) [31]. These extubation trials were not powered to evaluate the effect of the treatment on rates of survival without BPD.

(5) Many short-term adverse effects of dexamethasone therapy have been described; however, the main reason for the decline in its use is an adverse effect on neurodevelopment, particularly higher rates of CP. Eleven RCTs have been done to evaluate long term neurodevelopmental outcome (Table 2) [25, 40–48].

Table 2: Neurodevelopmental follow-up of dexamethasone RCTs reported after 2001.

Study, planned age at followup	Followup, % (no. of infants seen)	Treatment start time	Dexamethasone dosing regimen	Primary neurodevelopmental findings
McEvoy et al. [25], 1 year	66 (39)	At 7–21 days	High versus low dose: 7-day taper from 0.5 mg/kg/day versus 0.2 mg/kg/day	MDI < 70: 24% (high) versus 17% (low) (NS); CP: 10% versus 11% (NS)
Armstrong et al. [40], 18 months chronological age	96 (64)	On day 7	42-d taper versus 3-day pulse	No difference in 18-month outcomes No disability: 34% versus 31% (NS)
Doyle et al. [41], 2 years corrected age	98 (58)	After 7 days	0.15 mg/kg/day tapered over 10 days	Death or major disability: 46% versus 43% (NS); death or CP: 23% versus 37% (NS); CP: 14% versus 22% (NS); major disability 41% versus 31% (NS)
Stark et al. [42], 18–22 months corrected age	74 (123)	On day 1	0.15 mg/kg/day tapered over 7 days	MDI < 70: 51% versus 43% (NS); PDI < 70: 30% versus 35% (NS); abnormal neurologic exam: 25% each group
Romagnoli et al. [43], 3 years	100 (30)	On day 4	0.5 mg/kg/day tapered over 1 wk	No differences in any parameter; CP: 9% versus 14% (NS)
Wilson et al. [44], 7 years	84 (127)	Before 3 days	4 groups: 0.5 mg/kg/day tapered over 12 days versus late (15 days) selective, versus inhaled early or late selective	No difference in cognitive, behavioral, CP, or combined outcomes
Yeh et al. [45], school age (mean: 8 years)	92 (146)	On day 1	0.5 mg/kg/day for 1 wk, then tapered for a total of 28 days	Treated children were shorter ($P = .03$), had smaller head circumference ($P = .04$), lower IQ scores ($P = .008$), and more significant disabilities (CP, IQ < 5th percentile, vision or hearing impairment): 39% versus 22% ($P = .04$)
O'Shea et al. [46], 4–11 years	89 (84)	On day 15–25	0.5 mg/kg/day tapered over 42 days versus placebo	Death or major NDI: 47% versus 41% (NS); major NDI alone: 36% versus 14% ($P = .01$)
Gross et al. [47], 15 years	100 (22)	On day 14	0.5 mg/kg/day tapered over 42 days versus 18-day taper versus placebo	Intact survival (IQ > 70, normal neurologic exam, regular classroom): 69% versus 25% (18-d course) versus 18% (placebo) ($P < .05$)
Jones and the Collaborative Dexamethasone Trial Follow-up Group [48], 13–17 years	95 (150)	At 2–12 wk	0.5 mg/kg/day for 7 days	No difference in moderate/severe disability (defined as IQ > 2 SDs < mean, CP, hearing or vision loss); CP: 24% versus 15% (relative risk: 1.58 [95% confidence interval: 0.81–3.07])

NDI: neurodevelopmental impairment; PDI: psychomotor developmental index; NS: not significant.

The heterogeneity of these reports makes it problematic to combine them meaningfully. Some studies did not reveal adverse effects on neurodevelopmental outcomes at various ages, whereas others did. Most of the studies were small, which reduced their ability to either prove or disprove causation. Two RCTs that used low doses of dexamethasone revealed no significant increase in CP or other neurodevelopmental impairments when compared with placebo. Because only a total of 96 dexamethasone-treated infants were evaluated in these studies, the results must be interpreted with caution [41, 42].

(6) Cohort studies of dexamethasone have revealed an association of its use with impaired neurodevelopmental outcomes [48, 61]; however, such an association cannot be construed as definitive evidence of harm. A clinician's decision to use a therapy

incorporates numerous undocumented factors and varies from one clinician to the next, which may seriously confound the interpretation of such studies. Patients who receive dexamethasone for BPD are likely to be perceived as having more severe respiratory disease than infants who are not treated; such infants may have worse overall outcomes regardless of dexamethasone therapy.

(7) Authors of small series have also reported that infants treated with dexamethasone have more abnormalities on MRI than those not treated; again, causation cannot be attributed in the absence of an RCT [61, 62]. Two previously reported RCTs revealed more cranial ultrasound abnormalities in dexamethasone-treated infants compared with those treated with placebo, but the patient numbers were quite small [63, 64].

In summary, high daily doses of dexamethasone have been linked frequently to adverse neurodevelopmental outcomes, and this therapy is discouraged. Because an increase in adverse neurodevelopmental outcomes in treatment studies that used low doses of dexamethasone has not been reported, further studies of low-dose dexamethasone to facilitate extubation are warranted.

4.2. Hydrocortisone.

(1) Four RCTs designed to evaluate the ability of early hydrocortisone therapy to improve rates of survival without BPD have been done in recent times (Table 3) [49–52]. These studies were based on the premise that extremely preterm infants may have immature adrenal gland function, predisposing them to a relative adrenal insufficiency and inadequate anti-inflammatory capability during the first several weeks of life [21, 65–68]. In contrast to the heterogeneous nature of previous dexamethasone trials, these studies were similar in design, time of initiation, duration, and dose. The direction of effect favored the hydrocortisone-treated infants in all 4 studies, and a significant increase in rate of survival without BPD in the hydrocortisone-treated infants was reported for 2 of the studies. The largest trial ($n = 360$) did not reveal a significant benefit of hydrocortisone treatment in the overall study group; however, for infants exposed to prenatal inflammation ($n = 149$), identified before the trial as a specific group for analysis, hydrocortisone treatment resulted in a significant decrease in mortality rate and an increase in rate of survival without BPD [50]. Patient enrollment was halted early in 3 of these 4 studies because of a significant increase in spontaneous gastrointestinal perforation discovered in the largest trial [50], a complication also observed with early dexamethasone [68, 69]. The perforations may have resulted from an interaction between high endogenous cortisol concentrations and indomethacin therapy in the first 48 hours; however, because administration of indomethacin was not randomized, this hypothesis remains to be tested.

(2) Neurodevelopmental outcomes at 18 to 22 months' corrected age have been published for 3 of these trials, and no adverse effects of hydrocortisone treatment were found [70, 71]. In the largest multicenter trial, the incidence of death or major neurodevelopmental impairment (52% (hydrocortisone-treated) versus 56% (placebo)), major neurodevelopmental impairment alone (39% versus 44%), and CP (16% versus 18%) was similar [70]. The only significant findings favored the hydrocortisone-treated group and included a decreased incidence of a Bayley Scales of Infant Development (2nd edition) Mental Developmental Index (MDI) 2 SDs below the mean (MDI < 70, 27% versus 37%; odds ratio: 0.47 (95% confidence interval: 0.25–0.87)) and a higher incidence of awareness of object permanence (an early test of working memory and prefrontal executive function) (89% versus 79%; odds ratio: 2.19 (95% confidence interval: 1.06–4.52)).

(3) Hydrocortisone therapy given to facilitate extubation has been studied in cohort studies. In the first reported study, 25 infants treated with hydrocortisone at 1 hospital (5 mg/kg per day, tapered over 3 weeks) were compared with 25 untreated infants at the same hospital and additionally with a cohort of 23 infants treated with dexamethasone (0.5 mg/kg per day, tapered over 3 weeks) at a separate hospital [72]. The investigators found that hydrocortisone was as effective as dexamethasone in weaning infants from the ventilator and in decreasing supplemental oxygen therapy, with fewer short-term adverse effects. Followup of these children at school age revealed no differences in neurodevelopmental outcomes between hydrocortisone-treated infants and their comparison group, whereas dexamethasone-treated infants more often had an abnormal neurologic examination and less favorable school performance than their comparison cohort [72–75]. Subsequently, several large cohort studies from the same institution reported that although hydrocortisone-treated children were younger, smaller, and sicker than their untreated comparison groups, there were no adverse effects of hydrocortisone treatment on IQ, visual motor integration, memory testing, CP, or findings on MRI [74–76]. Investigators from this institution have also reported that neonatal dexamethasone but not hydrocortisone therapy resulted in long-lasting changes in hypothalamic-pituitary-adrenal axis and T-cell function [77].

4.3. Differences between Dexamethasone and Hydrocortisone. As discussed before, many RCTs have shown adverse neurodevelopmental outcomes after postnatal dexamethasone treatment for BPD, but neither multicenter RCTs nor cohort

Table 3: RCTs of early hydrocortisone to prevent BPD.

Study, no. of centers	*n*	Population: mechanically ventilated infants	Timing	Hydrocortisone dosing regimen	Rate of survival without BPD HC versus placebo, %
Watterberg et al. [49], 2 centers	40	BW: 500–999 g	<48 h postnatal age	0.5 mg/kg every 12 h for 9 days 0.25 mg/kg every 12 h for 3 days	60 versus 35 ($P = .04$)
Watterberg et al. [50], 9 centers	360	BW: 500–999 g	<48 h postnatal age	0.5 mg/kg every 12 h for 12 days 0.25 mg/kg every 12 h for 3 days	35 versus 34 (OR: 1.20 (95% CI: 0.72–1.99))
Peltoniemi et al. [51], 3 centers	51	BW: 501–1250 g	<36 h postnatal age	2.0 mg/kg/day tapered to0.75 mg/kg/day over 10 days	64 versus 46 (OR: 1.48 (95% CI: 0.49–4.48))
Bonsante et al. [52], 2 centers	50	BW: 500–1249 g	<48 h postnatal age	0.5 mg/kg every 12 h for 9 days; 0.25 mg/kg every 12 h for 3 days	64 versus 32 ($P < .05$)

studies have revealed adverse effects on functional or structural neurologic outcomes after neonatal hydrocortisone therapy. Possible reasons could be as follows.

(1) Dissimilar effective glucocorticoid dose-neonatal animal studies have consistently revealed adverse effects on brain growth after high doses of glucocorticoid [78, 79], and results of evaluation of 22 patients who received high-dose hydrocortisone in a study from the early 1970s were suggestive of harm [80, 81]. High-dose dexamethasone (0.5 mg/kg per day) is equivalent to at least 15 to 20 mg/kg per day of hydrocortisone [82], far higher than the doses of hydrocortisone given in the recent studies described previously. Low-dose dexamethasone (0.1–0.15 mg/kg per day) may be equivalent to 3 to 6 mg/kg per day of hydrocortisone; however, because of its much longer biological half-life, it could have a much higher relative potency [83]. Lowering the dose of dexamethasone may, therefore, decrease its adverse effects, as is suggested by the 2 studies of outcome after lower-dose dexamethasone therapy [41, 42].

(2) There are dissimilar effects of these agents on the hippocampus, an area of the brain critical to learning, memory, and spatial processing [84, 85]. The hippocampus contains a high density of both mineralocorticoid and glucocorticoid receptors [86, 87]. Hydrocortisone, which is identical to native cortisol, can bind to both classes of receptors. In contrast, dexamethasone binds only to glucocorticoid receptors, which, in animal models, has been shown to result in degeneration and necrosis of hippocampal neurons [88, 89]. This effect of dexamethasone is blocked by simultaneous administration of corticosterone (the cortisol equivalent in the rat) [88]. In humans, neonatal treatment with dexamethasone, but not hydrocortisone, has been shown to alter hippocampal synaptic plasticity and associative memory formation in later life [90]. Dexamethasone exposure has also been linked to decreased hippocampal volume in 1 cohort study [91, 92], but cohort studies of infants treated with hydrocortisone have revealed no decrease in hippocampal volume [74], no adverse effect on hippocampal metabolism, and no adverse effect on memory at school age [76] when compared with a larger, more mature group of nontreated infants.

Whatever the underlying explanation(s) for the observed differences in short- and long-term outcomes may be, further RCTs are needed to answer the many remaining questions, including whether lower doses of dexamethasone can avoid previously observed adverse effects, whether hydrocortisone is efficacious for extubation, whether specific groups of infants may derive particular benefit from hydrocortisone therapy, and whether the incidence of spontaneous gastrointestinal perforation during early glucocorticoid administration can be decreased by avoiding concomitant indomethacin or ibuprofen therapy and/or by monitoring cortisol concentrations.

4.4. Other Glucocorticoids (Systemic). No available evidence support use of other systemic glucocorticoids, such as prednisone or methylprednisolone, to treat or prevent BPD.

4.5. Inhaled Glucocorticoids. Although some tertiary care Neonatal ICUs routinely use inhaled beclomethasone for BPD babies, no available evidence support the efficacy of inhaled glucocorticoids to prevent or decrease the severity of BPD. Recent Cochrane database systemic review concluded "there is no evidence that inhaling steroids prevent chronic lung disease or the number of days the baby needed breathing support and additional oxygen" [93, 94].

Beclomethasone and flunisolide have been studied by nebulization in view of decreasing need for systemic steroid and side effects. The early postnatal administration of

inhaled steroid to prevent BPD was studied in a large randomized, multicenter trial [34]. In this study, 253 infants with a gestation age of <33 weeks, a birth weight of <1250 g, and who were mechanically ventilated at 3 to 14 days of age were randomly assigned to inhaled beclomethasone or a placebo for four weeks. The need for supplemental oxygen was similar in the beclomethasone and placebo groups at 28 days of life and 36 weeks postmenstrual age. In this study, beclomethasone therapy did not prevent BPD; however, it significantly reduced the use of systemic glucocorticoid therapy and mechanical ventilation at 28 days of age. In a small study, fluticasone propionate inhalation was given for 3 weeks to premature infants (less than 32 weeks) with moderate BPD (required fraction of inspired oxygen >0.25 or mechanical ventilation) at 28–60 days. There was no difference between infants treated with inhaled fluticasone versus placebo in the duration of oxygen therapy or ventilatory support [32].

4.6. Direct Intratracheal Instillation (IT) of Steroid with or without Surfactant as a Vehicle. Aerosolized drugs may be ineffective in preterm infants as very little drug is delivered to the lung, thereby limiting its effects. Novel idea of using surfactant as a vehicle to administer budesonide has been under study. A recent study by Halliday et al. demonstrated that intratracheal instillation of budesonide using surfactant as a vehicle significantly decreased the combined outcome of death and CLD without apparent immediate and long-term adverse effects [56]. Budesonide is a strong topical anti-inflammatory glucocorticoid. It can be effectively delivered to the lungs and remain in the lungs for some time after intratracheal instillation. Once absorbed, it can be rapidly metabolized to metabolites of low glucocorticoid effect. However, before this regimen can be recommended, a large sample trial is needed.

5. Current Evidence-Based Recommendations (AAP Revised Policy Statement, 2010)

(1) High daily doses of dexamethasone (approximately 0.5 mg/kg per day) have been shown to reduce the incidence of BPD but have been associated with numerous short- and long-term adverse outcomes, including neurodevelopmental impairment, and at present, there is no basis for postulating that high daily doses confer additional therapeutic benefit over lower-dose therapy.

Recommendation. In the absence of randomized trial results showing improved short- and long-term outcomes, therapy with high-dose dexamethasone cannot be recommended.

(2) Low-dose dexamethasone therapy (<0.2 mg/kg per day) may facilitate extubation and may decrease the incidence of short- and long-term adverse effects observed with higher doses of dexamethasone. Additional RCTs sufficiently powered to evaluate the effects of low-dose dexamethasone therapy on rates of survival without BPD, as well as on other short- and long-term outcomes, are warranted.

Recommendation. There is insufficient evidence to make a recommendation regarding treatment with low-dose dexamethasone.

(3) Low-dose hydrocortisone therapy (1 mg/kg per day) given for the first 2 weeks of life may increase rates of survival without BPD, particularly for infants delivered in a setting of prenatal inflammation, without adversely affecting neurodevelopmental outcomes. Clinicians should be aware of a possible increased risk of isolated intestinal perforation associated with early concomitant treatment with inhibitors of prostaglandin synthesis. Further RCTs powered to detect effects on neurodevelopmental outcomes, aimed at targeting patients who may derive most benefit and developing treatment strategies to reduce the incidence of isolated intestinal perforation, are warranted.

Recommendation. Early hydrocortisone treatment may be beneficial in a specific population of patients; however, there is insufficient evidence to recommend its use for all infants at risk of BPD.

(4) Higher doses of hydrocortisone (3–6 mg/kg per day) instituted after the first week of postnatal age have not been shown to improve rates of survival without BPD in any RCT. RCTs powered to assess the effect of this therapy on short- and long-term outcomes are needed.

Recommendation. Existing data are insufficient to make a recommendation regarding treatment with high-dose hydrocortisone.

6. Summary

BPD is the disease of very low birth weight and extremely low birth weight newborns with multifactorial etiology including prematurity itself, ventilator-induced injury, oxygen, and inflammation. BPD has long-term adverse pulmonary and neurodevelopment outcome. Steroids usage for treatment of BPD also has been shown to have adverse neurodevelopmental outcome. Available data are conflicting and inconclusive; clinicians must use their own clinical judgment to balance the adverse effects of BPD with the potential adverse effects of treatments for each individual patient. Very low birth weight infants who remain on mechanical ventilation after 1 to 2 weeks of age are at very high risk of developing BPD [58]. When considering corticosteroid therapy for such an infant, clinicians might conclude that the risks of a short course of glucocorticoid therapy to mitigate BPD are warranted [59]. This individualized decision should be made in conjunction with the infant's parents.

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