Respiratory Care Year in Review 2010: Part 2. Invasive Mechanical Ventilation, Noninvasive Ventilation, Pediatric Mechanical Ventilation, Aerosol Therapy

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Summary

The purpose of this paper is to review the recent literature related to invasive mechanical ventilation, NIV, pediatric mechanical ventilation, and aerosol therapy. Topics covered related to invasive mechanical ventilation topics include the role of PEEP in providing lung protection during mechanical ventilation, unconventional modes for severe hypoxemia, and strategies to improve patient-ventilator interactions. Topics covered related to NIV include real-life NIV use, NIV and extubation failure, and NIV and pandemics. For pediatric mechanical ventilation, the topics addressed are NIV, invasive respiratory support, and inhaled nitric oxide. Topics covered related to aerosol therapy include short-acting β -adrenergic agents, long-acting β -adrenergic agents, long-acting antimuscarinic agents, inhaled corticosteroid therapy, phosphodiesterase type 4 (PDE4) inhibitors, long-acting β -adrenergic plus inhaled corticosteroid, long-acting antimuscarinic plus

inhaled corticosteroid, nebulized hypertonic saline, inhaled mannitol, and inhaled antibiotic therapy. These topics were chosen and reviewed in a manner that is most likely to have interest to the readers of *RESPIRATORY CARE*. *Key words:* aerosol therapy; airway pressure release ventilation; high-frequency oscillatory ventilation; inhaled bronchodilator; inhaled corticosteroid; mechanical ventilation; noninvasive ventilation. [Respir Care 2011;56(5):667–680. © 2011 Daedalus Enterprises]

Introduction

It can be difficult to remain abreast of new evidence. It can be an even greater challenge to filter the literature to what is clinically relevant to one's practice and to update one's practice based on the most recent evidence. At the 56th International Respiratory Congress, members of the *RESPIRATORY CARE* editorial board presented a series of papers in the theme of "Year in Review." Topics were chosen that are likely to have special interest to the readers of *RESPIRATORY CARE*. We are pleased to publish these in 2 parts in the Journal. Part 1 has been published.¹ In this, Part 2, we cover invasive mechanical ventilation, noninvasive ventilation (NIV), pediatric mechanical ventilation, and aerosol therapy.

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Invasive Mechanical Ventilation in the Adult

The Role of PEEP in Providing Lung Protection During Mechanical Ventilation

PEEP is a two-edged sword. On the one hand, in lung units that can be recruited, appropriate application of PEEP maintains alveolar stability. This improves gas exchange and lung compliance. Additionally, preventing repetitive collapse and re-opening is thought to reduce ventilator-induced lung injury. On the other hand, especially in lungs that have little or no recruitment potential, PEEP over-distends lung units, especially healthier or more normal lung units. There are a number of approaches to setting PEEP to balance recruitment against over-distention. Ideally, imaging techniques such as computed tomography, or perhaps electrical impedance tomography, could allow clinicians to visually balance recruitment potential with over-distention risk. Unfortunately these techniques are expensive and not generally available.

Many clinicians argue that analyzing the mechanical properties of the respiratory system could balance these 2 PEEP effects. Examples of this concept include using the pressure-volume curve of the lungs to define collapse and over-distention points, using incremental or decremental PEEP titration maneuvers to determine best compliance, or using the airway pressure profile during a constant inspiratory flow to assess recruitment and/or over-distention (the stress index). However, these techniques require special expertise, they are time-consuming, and the results can be difficult to interpret. They are thus not routinely used in most intensive care units (ICUs).

Gas exchange is probably the most common tool used to assess PEEP settings. In using a gas exchange approach, the clinician tries to balance PEEP application with F_{IO_2} exposure, while limiting plateau pressure and maintaining an adequate, but not maximal, P_{aO_2} (for example, 55–80 mm Hg). With this approach there are 2 fundamentally different prioritization approaches. The first is that PEEP increases should be prioritized over F_{IO_2} increases to address hypoxemia. The alternative is to prioritize F_{IO_2} over PEEP. The former focuses on the recruitment benefit of PEEP, while the latter focuses on limiting over-distention from PEEP.

Over the past 10 years, 3 large clinical trials have addressed these different PEEP/ F_{IO_2} prioritization approach-

es: the Acute Respiratory Distress Syndrome (ARDS) Network ALVEOLI trial,² the Canadian LOVS trial,³ and the European EXPRESS trial.⁴ Each trial compared PEEP- F_{IO_2} algorithms that either prioritized PEEP over F_{IO_2} (high-PEEP strategy) or F_{IO_2} over PEEP (low-PEEP strategy). The 3 trials adhered to a low-tidal-volume lung-protective strategy, and each targeted modest rather than maximal P_{aO_2} . In each of these trials, there were trends toward benefit with a high-PEEP strategy, but none reached statistical significance in terms of meaningful clinical outcomes such as mortality.

In 2010 a study was reported that combined all of the patients in these 3 trials into a single database.⁵ A priori, patients were defined as having either a severe lung injury (those meeting ARDS criteria) or a less severe lung injury (those meeting only acute lung injury [ALI] criteria). In the pooled analysis, the high-PEEP strategy was shown to have a statistically significant mortality benefit, but only in the patients with ARDS. In contrast, the high-PEEP strategy was associated with a worse mortality in patients with less severe lung injury (although this did not reach statistical significance). Taken together, these results strongly suggest that, when using gas exchange criteria and balancing PEEP and F_{IO_2} , aggressive high-PEEP strategies seem appropriate in those patients with severe injury, while the conservative low-PEEP strategies seem more appropriate in those with less severe lung injury.

These results are provocative and support the use of different PEEP- F_{IO_2} prioritization schemes, depending on the degree of lung injury. However, imaging studies of acutely injured lungs suggest that a more logical approach might be to determine lung recruitability and reserve high-PEEP strategies for highly recruitable lungs and low-PEEP strategies for the less recruitable lungs. Further studies are needed to validate this concept.

Unconventional Modes for Severe Hypoxemia

Patients with severe hypoxemic respiratory failure requiring potentially injurious ventilator settings such as plateau pressure > 30 cm H_2O , tidal volume > 8 mL/kg ideal body weight, and/or $F_{IO_2} > 0.60$ – 0.70 are a clinical challenge. One technique proposed for this problem is the use of airway pressure release ventilation (APRV). APRV uses a long inspiratory time and a short expiratory time to elevate mean airway pressure (and thus improve ventilation-perfusion matching) without elevating end-inspiratory plateau pressure. APRV also allows spontaneous breaths during this long inflation period, and this is thought to prevent dependent atelectasis and enhance gas mixing.

A number of observational studies have shown that APRV does raise mean airway pressure without necessarily raising applied end-inspiratory pressure, and that gas exchange is enhanced.⁶ However, few clinical trials have

evaluated meaningful outcomes with this mode, especially when compared to accepted lung-protective ventilatory strategies.

In 2010, 2 clinical outcome studies of APRV were reported. The first compared APRV to ARDS Network low-tidal-volume ventilation in 64 patients with trauma-induced ALI/ARDS.⁷ In this study there were no significant differences in any of the clinical outcomes. Specifically, ventilator days, ICU stay, and mortality were comparable regardless of mode. The second study was a retrospective evaluation of ventilator utilization in 349 ICUs.⁸ This study was a re-analysis of the database of a very large ventilator usage survey reported previously.⁸ In this study, 234 patients were identified who were receiving APRV. A case control group of matched patients based on a propensity score and who were receiving continuous mandatory ventilation was also identified. Comparing the APRV group with the matched continuous mandatory ventilation group found no differences in mortality, ventilator-free days, or stay. Taken together, these 2 studies suggest that APRV, while a physiologically interesting mode, does not seem to be associated with meaningful clinical outcome benefits in patients with severe ARDS.

Another approach to managing severely hypoxemic patients with ALI is high-frequency oscillatory ventilation (HFOV). HFOV applies substantial mean airway pressure, but applies very little pressure or volume fluctuations in the alveolus. It is thus sometimes referred to as “CPAP with a wiggle.” HFOV has been used in pediatric and neonatal respiratory failure for decades. Data from adults, however, are few, and firm conclusions have been difficult. In 2010, the McMaster University Evidence Based Medicine Group updated a meta-analysis of HFOV in ARDS.⁹ They analyzed 8 clinical trials of HFOV in patients with ARDS. These included pediatric as well as adult patients who met criteria for ARDS. In this analysis, 6 of the 8 studies applied HFOV within 48 hours of intubation, and in 5 of the 8 studies the ARDS Network low-tidal-volume strategy¹⁰ was used as the control group. There were 419 patients included in these studies. None of the trials alone showed a significant reduction in mortality, but the meta-analysis did show a mortality benefit. HFOV was associated with a significant reduction in mortality, with a risk ratio (RR) of 0.77 and a 95% CI from 0.61–0.98. This suggests that there may be a role for HFOV in severe respiratory failure from ARDS. However, the numbers are small, pediatric patients were included, and the combined results barely reached statistical significance. The results of ongoing studies of HFOV should provide more solid data in the future.

A variation on high-frequency ventilation is high-frequency percussive ventilation (HFPV), a technique that uses high-frequency pressure pulses superimposed on a conventional ventilation pattern. This technique is thought

to do 2 things. First, the high-frequency pulsations may enhance gas mixing and thus gas exchange. Second, the high-frequency pulses may enhance secretion clearance. Indeed, it is this latter benefit that has driven its popularity in burn units, where supporters claim improved pulmonary hygiene in patients with airway burns. One of the few randomized trials with this technique was reported in 2010.¹¹ This study was conducted in a military burn unit, in which 62 patients were randomized to HFPV or a conventional lung-protective ventilator strategy. Approximately one third of the patients had substantial inhalational injuries. Although the HFPV group met gas exchange goals more rapidly, the ultimate outcomes in terms of survival, ventilator-free days, and hospital stay were not statistically different. HFPV thus remains an attractive theoretical adjunct, especially in patients with severe airway burns, but evidence supporting improved outcomes from its use is lacking. Of note, a recent paper published in *RESPIRATORY CARE* suggests that, in the setting of ALI, typical HFPV settings may deliver injurious tidal volume.^{12,13} Further study is needed of the potential benefits, or deleterious effects, of HFPV.

Improving Patient-Ventilator Interactions

A number of clinical studies in mechanically ventilated patients over the last 2 decades have suggested that allowing patient muscle activity is useful. Specifically, if the muscle activity is comfortable and non-fatiguing, it can prevent ventilator muscle atrophy and facilitate ventilator discontinuation. The general clinical consensus has thus been to allow comfortable muscle activity as soon as possible. However, an interesting study in 2010 has challenged this notion by showing that 48 hours of routine use of neuromuscular blockers in severe respiratory failure resulted in a lower mortality than in similar patients not receiving these agents.¹⁴ This study, however, is difficult to interpret in that several unusual things occurred. First, they used rescue neuromuscular blockers in over half of the control group. The reasons for this are not clear. There also appears to be a very high pneumothorax rate in the control group, which was not explained. Finally, there was a very unusual pattern to the mortality data. Specifically, no mortality difference was noted for the first 2 weeks of the trial, and then, during a very brief period in the third week, the 2 mortality curves separate dramatically, only to return to comparability soon thereafter. This pattern of mortality is difficult to link to 2 days of neuromuscular blocker 2 weeks earlier. Thus, although the results must be taken seriously, it seems premature to recommend routine use of neuromuscular blockade in early ALI.

The above trial notwithstanding, many clinicians accept the concept that active, non-fatiguing, comfortable patient muscle activity is preferable to absent patient muscle ac-

tivity. In this regard, 2 interesting modes developed over the last few years are worthy of comment. The first is proportional assist ventilation, a mode that calculates the patient's respiratory system mechanics and then applies pressure and flow in proportion to effort. The second is neurally adjusted ventilatory assistance (NAVA), a mode in which pressure and flow delivery is driven by a diaphragmatic electromyogram signal measured via an esophageal catheter. Proportional assist ventilation should improve flow and cycle synchrony, whereas NAVA should address both of these as well as trigger synchrony. In 2010 there were disappointingly few new data on these 2 modes. Indeed, the most interesting developments in proportional assist ventilation involved noninvasive applications that showed exercise improvement in patients with obesity or patients with idiopathic pulmonary fibrosis.^{15,16} With NAVA there were only 3 small observational studies with crossover designs that seemed to support the notion that NAVA better matched patient effort.¹⁷⁻¹⁹ The issues related to patient-ventilator interactions are thoroughly presented in a *RESPIRATORY CARE* Journal Conference, conducted in 2010 and published in 2011.²⁰

Noninvasive Ventilation

Real-Life Noninvasive Ventilation Use

An internet-based survey using a 41-question, self-administered questionnaire was developed by Bierer et al²¹ and sent to respiratory therapists (RTs) and critical care physicians (MDs) selected from 3 hospitals in each of 21 Veterans Affairs networks, based on severity of patient mix, level of staffing, and work load. Previous experience and training in NIV was limited. NIV was reported to be widely available and applied in both monitored and unmonitored settings. NIV was identified as a first-line option for COPD and congestive heart failure, but perceived use was less than ideal. Compared to 29% of physicians, 64% of the RTs felt NIV was used < 50% of the time when indicated. Larger ICUs reported more frequent use of NIV than smaller ICUs. Written guidelines were noted by 65% of respondents, but only 27% had titration guidelines. The perceived efficacy of NIV was low, with a success rate of > 50% noted by only 29% of respondents. Bierer et al concluded that the perception of NIV use in the Veterans Affairs hospitals varies significantly and revealed a wide range of training and experience, location of use, presence of written guidelines, and methods of delivery. Indeed, perceptual differences existed between RTs and MDs.

Hess et al²² conducted a Web-based survey of 132 academic emergency departments (EDs) in the United States, with an impressive response rate of 90%. It was found that 64% of MDs and 99% of RTs were very familiar with

NIV. The RTs were primarily responsible for initiation of NIV (96% of cases), and NIV was used one or more times per week in 92% of the EDs. NIV was more commonly used for exacerbation of COPD and congestive heart failure, compared to acute asthma. The majority of respondents reported the perception that the use of NIV was about right for each of the diagnoses. NIV equipment was available in 76% of EDs, and it was initiated in less than 20 min in the majority of them. Bi-level ventilators and oronasal mask were more frequently used. Barriers to greater use of NIV in the ED include MD familiarity, availability of an RT and equipment in the ED, and time required for NIV.

Crimi et al²³ reported data from a Web-based survey sent to 530 MDs, designed to assess current NIV practices in Europe and in different case scenarios, placing emphasis on the technical aspects of NIV use. The response rate was 51%. The NIV utilization rate was higher for pulmonologists (52.9% reported > 20% of ventilated patients treated with NIV per year) than intensivists and anesthesiologists. The most common indication for all the physicians was COPD exacerbation (48%). Physicians were more likely to use an NIV-dedicated ventilator in COPD exacerbation and cardiogenic pulmonary edema. An ICU ventilator with NIV module was preferred in de novo hypoxemic respiratory failure and post-extubation scenarios, mainly because of the ability to use a dual-limb circuit and inspiratory oxygen control. Stand-alone CPAP was used only for cardiogenic pulmonary edema. Overall, the oronasal mask was the most frequently used interface, irrespective of clinical scenarios, with a limited use of the helmet (only for cardiogenic pulmonary edema). No major geographical differences were observed.

These 3 studies indicate that NIV is still underutilized in real life, especially in the ICU, while a relatively high proportion of patients in the ED or respiratory units are presently treated with NIV, especially for the treatment of ARF due to COPD exacerbation and cardiogenic pulmonary edema. Due to the different healthcare system and educational program, RTs are very much involved in the NIV delivery in the United States, while in Europe this is performed by MDs.

NIV and Extubation Failure

Extubation attempts may fail in as many as 23.5% of patients, and the in-hospital mortality of these patients may reach 30–40%.²⁴ The cause of extubation failure and the time elapsed before re-intubation are independent predictors of outcome.²⁵

Ferrer et al²⁶ performed a multicenter randomized controlled trial specifically designed for patients who developed hypercapnia during a spontaneous breathing trial. Patients were randomly assigned to receive NIV or con-

ventional oxygen therapy after a successful spontaneous breathing trial. The primary end point was to avoid respiratory failure within 72 hours of extubation. They found that respiratory failure was less frequent in the NIV group than in the other (15% vs 25%). NIV was independently associated with a lower risk of respiratory failure after extubation. In patients with respiratory failure, NIV as a rescue therapy avoided re-intubation. The overall 90-day mortality was significantly lower in the group of NIV (11% vs 31%).

Over a period of 3 years, Boeken et al²⁷ analyzed all patients extubated within 12 hours after cardiac surgery, in whom P_{aO_2}/F_{IO_2} deteriorated without hypercapnia. All patients met predefined criteria for re-intubation; 125 patients required immediate re-intubation, 264 received CPAP, and 36 were treated with NIV. Of patients in the later groups, 26% and 22.2%, respectively, were intubated after an unsuccessful CPAP or NIV attempt. Immediate re-intubation was associated with higher mortality (8.8% vs 4.2% and 5.6%, respectively), a higher incidence of pulmonary infections, and a high need for catecholamines. Boeken et al concluded that re-intubation after cardiac operations should be avoided, because CPAP and NIV are safe and effectively improve arterial oxygenation in most patients with non-hypercapnic oxygenation failure.

The different study designs suggest that, while NIV can be safely utilized to prevent the need of re-intubation when hypercapnia is present at the time of extubation, we still need further randomized controlled studies before adopting the use of NIV to treat extubation failure after major cardiac surgery.

NIV and Pandemics

An observational study²⁸ of patients with confirmed or probable 2009 influenza A (H1N1) and respiratory failure in 96 patients requiring mechanical ventilation was performed in Spanish-speaking countries. Shock and ARDS were diagnosed during the first 72 hours of admission in 43% and 72% of patients, respectively. The overall mortality rate was 50%. NIV was used on admission in 43 patients (45%), being unsuccessful in 33 (77%) patients. Despite the low success rate, this descriptive study suggests that NIV may be applied in this condition, particularly in the less severe patients (higher P_{aO_2}/F_{IO_2}). These results are consistent with the recommendations of 2 European societies (European Respiratory Society and European Society of Intensive Care Medicine), who suggested the use of NIV during H1N1 only in a specific subset of patients and with some practical cautions.²⁹ The American Association for Respiratory Care, however, has recommended that NIV should not be used to treat acute respiratory failure secondary to H1N1.³⁰

Pediatric Mechanical Ventilation

Pediatric mechanical ventilation encompasses a wide variety of disease processes and patient sizes. Clinicians involved with the respiratory care of pediatric patients may care for an adult-sized pediatric patient one moment and a low-birth-weight pre-term neonate the next. Thus, pediatric clinicians represent a versatile group of individuals with unique clinical challenges. As of now, there are scant experimental data to suggest any disease-specific standardized approaches for initiating and managing mechanical respiratory support in pediatrics. It is also unclear whether one form of support or airway interface is more beneficial than another. Thus, clinicians caring for pediatric patients have grown accustomed to individualizing the ventilation strategy based on adequacy of gas exchange, work of breathing (WOB), and observing other pathophysiologic changes in the patient.

Many of the same fundamental concepts that embrace lung-protective conventional mechanical ventilation and ventilator liberation in adults are being applied, with some modification, in pediatrics as well. As the old adage goes, children are not little adults; thus, ventilator approaches that have traditionally worked well in adults may not work well in all pediatric patients. It is with some conjecture that the much-needed pediatric ventilator research has been recently overshadowed by important adjuncts to mechanical ventilation, including inhaled nitric oxide, surfactant replacement therapy, and extracorporeal membrane oxygenation. Fortunately, non-profit groups such as the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI)³¹ and the Vermont Oxford Network,³² and governmental groups such as the Eunice Kennedy Shriver National Institute of Child Health and Human Development³³ have developed coordinated programs of research, education, and quality improvement, with a common goal of improving the care and health outcomes of critically ill infants and children. There are several large randomized controlled trials, educational programs, and forums that have been conducted by these groups to better inform clinicians on state-of-the-art in pediatric mechanical ventilation practices.

In 2010, the results from several clinical trials, bench studies, comprehensive meta-analyses, and evidence-based expert opinion summaries were published. These findings will undoubtedly reshape future clinical practice and generate new research questions for years to come. A PubMed search was conducted using the following search terms: “pediatric mechanical ventilation” with limits of English language, human studies, all child (0–18 y) and “infant mechanical ventilation” with limits of English language, human studies, all infant (0–23 months). In a few cases, results from bench and animal studies will be discussed.

Noninvasive Ventilation

The majority of the pediatric ventilation research published in 2010 was focused more on neonatal NIV strategies than any other aspect of respiratory care. The improved understanding of lung injury related to endotracheal tubes³⁴ and mechanical ventilators³⁵ has prompted clinicians to identify support strategies to avoid invasive mechanical ventilation. Pre-term neonates represent the largest population of pediatric patients requiring respiratory intervention. They are born with fluid-filled, underdeveloped lungs that lack mature surfactant and are extremely susceptible to injury, even in the absence of mechanical respiratory support. Additionally, pre-term neonates are prone to developing atelectasis and may not be able to generate the necessary energy to provide adequate lung inflation or maintain end-expiratory lung volume. The majority of the latest research from 2010 was focused on evaluating outcomes in neonates based on respiratory therapy interventions that are initiated in the delivery room or within the first few hours of life.

Lista et al³⁶ evaluated outcomes in pre-term neonates with respiratory distress over a 2-year period prior to and following the implementation of sustained lung inflations in the delivery room. In the first phase of the study, neonates were treated in the delivery room, as recommended by the American Academy of Pediatrics (retrospective control group, $n = 119$). During the following 2-year period, infants were treated with sustained lung inflation in addition to the American Academy of Pediatrics recommendations (prospective, sustained-lung-inflation group, $n = 89$). The sustained-lung-inflation group received 25 cm H₂O inflation with a T-piece resuscitator (Neopuff, Fisher & Paykel, Auckland, New Zealand) for 15 s and/or repeated if the newborn's breathing was insufficient, heart rate < 100 beats/min, cyanotic, or unable to maintain $S_{pO_2} > 80\%$ with $F_{IO_2} > 0.5$. Both groups were supported using nasal CPAP and intubated for pH < 7.20 , $P_{aCO_2} > 65$ mm Hg, or $P_{aO_2} < 50$ mm Hg, with $F_{IO_2} > 0.5$ and intractable apnea. The sustained-lung-inflation group had less need for ($P < .001$) and shorter duration of mechanical ventilation ($P = .008$), a more frequent occurrence of exclusive nasal CPAP use ($P < .001$) and INTubation-SURfactant-Extubation (INSURE) treatment ($P = .01$), less need for surfactant ($P = .03$) and postnatal steroids ($P = .01$), a shorter duration of oxygen therapy ($P = .02$), and a lower occurrence of chronic lung disease in survivors ($P = .004$) than the control group. Based on this study and another recent report,³⁷ sustained lung inflations represent a simple, safe, and effective option for recruiting air-spaces, establishing functional residual capacity, and reducing the need for additional respiratory intervention in pre-term neonates.

Nasal CPAP is a gentle form of respiratory support that promotes spontaneous breathing around a continuous distending pressure, using short bi-nasal prongs. A large multicenter randomized controlled trial (the SUPPORT trial) was conducted using a 2-by-2 factorial design to evaluate outcomes in pre-term neonates (24–27 weeks gestational age) assigned to intubation and early surfactant treatment ($n = 653$) or nasal CPAP treatment in the delivery room ($n = 663$).³⁸ Neonates were subsequently managed using a protocol-driven limited-ventilation strategy with extubation to nasal CPAP. There were no differences in the primary outcome of chronic lung disease ($P = .07$) or death ($P = .09$) between the groups. However, neonates treated initially with nasal CPAP had a lower need for mechanical ventilation ($P = .03$) and postnatal corticosteroids ($P < .001$), and had greater survival without the need for HFOV or conventional ventilation at 7 days ($P = .01$) than did the early-surfactant group.

In another study,³⁹ the same patients from the previous SUPPORT (2-by-2 factorial design) trial were also enrolled in a concurrent study to evaluate the primary outcome of retinopathy of prematurity in pre-term neonates randomized to an S_{pO_2} target range of 85–89% ($n = 652$) or 91–95% ($n = 662$). There were no differences in the primary combined outcome of severe retinopathy of prematurity or death between the 2 groups ($P = .21$). Death before discharge was lower in the higher S_{pO_2} range than the lower S_{pO_2} range ($P = .04$). Retinopathy of prematurity among survivors who were discharged or transferred to another facility or who reached the age of 1 year was lower in the lower- S_{pO_2} group than the higher- S_{pO_2} group ($P < .001$). There are several other large multicenter trials underway that will provide additional information about outcomes, using similar oxygenation strategies.

The CURPAP study⁴⁰ was another randomized controlled trial that randomized pre-term neonates 25–38 weeks gestational age to intubation, to prophylactic surfactant treatment and immediate extubation to nasal CPAP at 1 hour (early-surfactant group, $n = 105$) or early nasal CPAP treatment and selective use of surfactant (early-nasal-CPAP group, $n = 103$) for signs of respiratory failure. There were no differences in the primary or secondary outcomes between the 2 groups (in other words, death, chronic lung disease, intraventricular hemorrhage, duration of ventilation). Infants who were treated with prophylactic surfactant tended to have a higher rate of pneumothorax, compared with the nasal-CPAP group (6.7% vs 1.0%) but did not reach statistical significance.

An important observation from the previous reports is that not all infants can be supported effectively with nasal CPAP alone. Approximately 67% of infants from the SUPPORT trial³⁸ and 31–34% from the CURPAP trial⁴⁰ failed nasal CPAP and required subsequent intubation and mechanical ventilation and surfactant administration. Com-

mon questions that clinicians are faced with are whether different nasal CPAP systems may affect these outcomes differently and whether noninvasive devices capable of providing greater levels of respiratory support should be used in infants who would otherwise fail nasal CPAP.

In a randomized crossover design study, Courtney et al⁴¹ compared differences in WOB and gas exchange between bubble nasal CPAP and ventilator nasal CPAP at equivalent nasal prong pressure in 18 pre-term infants with mild respiratory distress syndrome. The WOB and most respiratory parameters were not different in neonates when the devices were being used. However, the transcutaneous oxygen levels were higher during bubble nasal CPAP than ventilator nasal CPAP ($P < .001$). The reasons for this are not clear, but it has been speculated that the bubbles, created during bubble CPAP, transmit small-amplitude, high-frequency airway pressure oscillations to the lungs⁴² that may enhance gas exchange and alveolar recruitment.⁴³

In 2010, there were 2 reports^{44,45} of a novel high-amplitude bubble CPAP system that is capable of providing a greater level of respiratory support than conventional bubble CPAP alone. It was found that controlling the angle through which gas enters the CPAP water-seal column greatly enhances the oscillations in the airway pressure at the nasal airway interface to meet the changing requirements of patients with worsening respiratory distress. In a neonatal lung model affixed with leaky nasal prongs, the high-amplitude bubble-CPAP device adjusted with the outlet tubing at 135°, in relation to the water surface level, was found to deliver similar tidal volumes as those previously measured during HFOV in infants.⁴⁵ In addition, it was demonstrated that high-amplitude bubble-CPAP provides noninvasive support, via nasal prongs, to spontaneously breathing, lung-lavaged juvenile rabbits with lower WOB ($P < .001$) and higher P_{aO_2} ($P < .007$) than were observed in the same animals supported with bubble nasal CPAP at identical mean airway pressures.⁴⁵ Two rabbits supported by high-amplitude bubble-CPAP became apneic with normal P_{aCO_2} and vital signs. High-amplitude bubble-CPAP may represent a relatively simple new strategy for supporting a greater fraction of neonates who would otherwise fail nasal CPAP and require invasive mechanical ventilation. Clinical trials will be needed in human neonates to test this hypothesis in the future.

Sigh positive airway pressure (SiPAP, CareFusion, Yorba Linda, California) is a form of noninvasive respiratory support that assists spontaneously breathing neonates by alternating between 2 preset CPAP levels. The goal of this therapy is to augment tidal volume, increase functional residual capacity, reduce apnea, and reduce the need for invasive mechanical ventilation. Prior to 2010 there had been very little research performed using the SiPAP device. In 2010 there were 2 clinical studies in neonates involving SiPAP.

Ancora et al⁴⁶ retrospectively evaluated whether SiPAP following surfactant administration and brief ventilation prevented re-intubation and mechanical ventilation in pre-term neonates. Neonates in the historical control group were supported with 4–6 cm H₂O nasal CPAP ($n = 22$), and neonates in the SiPAP group ($n = 38$) were managed using P_{low} 4–6 cm H₂O, P_{high} 5–8 cm H₂O, T_{high} 0.5–0.6 s, and 10–30 cycles/min. The need for mechanical ventilation was greater in the historical control group than in the SiPAP group (27% vs 0%, $P = .001$). It is important to note that the SiPAP group received antenatal steroids more frequently than the historical control group ($P = .003$), which may also explain why there was no need for re-intubation in the SiPAP group. Nonetheless, SiPAP combined with antenatal steroids and surfactant appears to be an attractive initial clinical approach for pre-term neonates.

Lista et al⁴⁷ conducted a randomized controlled trial to evaluate outcomes in pre-term neonates using nasal CPAP ($n = 20$) or SiPAP ($n = 20$) as an initial form of support in the acute phase of respiratory distress syndrome. All enrolled infants received sustained lung inflations in the delivery room and surfactant (as needed) with immediate extubation. Neonates in the nasal CPAP group were supported with nasal CPAP 6 cm H₂O, and the settings in the SiPAP group were adjusted to provide a similar mean airway pressure as the nasal CPAP group (~6 cm H₂O). Plasma serum levels of pro-inflammatory cytokines (interleukin-6, interleukin-8, tumor necrosis factor alpha) were obtained to observe whether there were differences in lung injury between the 2 groups. Infants supported by SiPAP underwent shorter duration of mechanical ventilation ($P = .03$), less O₂ dependence ($P = .03$), and were discharged sooner ($P = .02$) with similar serum cytokine levels as the group supported initially with nasal CPAP. Results from this study suggest that SiPAP provides a more beneficial form of noninvasive support than nasal CPAP at similar mean airway pressure, without increasing lung-injury.

Prior to SiPAP, the most commonly used form of neonatal NIV was accomplished using the Infant Star ventilator (Covidien, Mansfield, Massachusetts). The Star-Synch module provided patient-triggered ventilation, using a Graseby capsule placed on the abdomen. This represented an effective way to trigger ventilator breaths, independent of the leak created at the mouth or nasal airway interface. Since 2006 the Infant Star ventilator has been discontinued and is no longer being used. In the United States SiPAP has an integrated Graseby capsule that serves only to monitor respiratory rate. However, in Canada and Europe the Graseby capsule allows patient-trigger of P_{high} . It is unclear when or if this feature will be approved in the United States. Investigators are evaluating the effective-

ness and physiologic benefits related to patient-trigger with this form of support.

Invasive Respiratory Support

A large proportion of neonates initially supported with noninvasive techniques require endotracheal intubation and invasive mechanical ventilation. There have been many new advances in pediatric ventilator technology over the last decade, including patient-triggered ventilation, volume-targeted ventilation, and improved tidal-volume monitoring at the proximal airway. Prior to 2010 there was very little evidence to suggest that these advances have resulted in improved incomes in neonates. As such, time-cycled, pressure controlled ventilation (PCV) has been the most frequently used form of mechanical ventilation in pediatrics for nearly 40 years.

In a recent publication from the NeoVent group,⁴⁸ 173 neonatal ICUs in 21 European countries participated in a survey that included 535 pre-term neonates. Clinicians caring for ventilated pre-term neonates used conventional ventilation (85%) more frequently than high-frequency ventilation (15%). During conventional ventilation the preferred mode of choice was patient-triggered, time-cycled PCV (79%) with almost exclusive use of tidal-volume monitoring at the proximal airway. Only 11% of clinicians used modes that provide some form of volume-targeted strategy, including volume control ventilation or dual-control ventilation. In the United States there have been no studies designed to assess ventilator approaches in neonates, but it is likely that they are similar to those practiced in Europe.

A recent Cochrane review from 2010,⁴⁹ consisting of 7 parallel trials, including 555 patients, had an intervention period of 72 hours, using either volume-targeted (volume control ventilation; dual-control ventilation) or PCV during conventional mechanical ventilation. The use of volume-targeted modes resulted in a reduction in the combined outcome of death or chronic lung disease (RR 0.73 95% CI 0.57–0.93), number needed to treat 8 (95% CI 5–33). Volume-targeted modes also resulted in reductions in pneumothorax (RR 0.46, 95% CI 0.25–0.84), number needed to treat 17 (95% CI 10–100); days of ventilation (mean difference –2.36, 95% CI –3.9 to –0.8); hypocarbia (typical RR 0.56, 95% CI 0.33–0.96), number needed to treat 4 (95% CI 2–25); and the combined outcome of periventricular leukomalacia or grade 3–4 intraventricular hemorrhage (typical RR 0.48, 95% CI 0.28–0.84), number needed to treat 11 (95% CI 7–50).

During volume-targeted ventilation, neonates from this meta-analysis were supported with 7 different ventilators and 6 different volume-targeting modes. However, each of these modes is inherently different and there are no human studies that have demonstrated that one volume-targeted mode is superior to another. More importantly, it is un-

clear why more clinicians are not choosing volume-targeted strategies over PCV in neonates as an initial form of support for conventional ventilation. One notion may be that previous attempts at neonatal volume-targeted ventilation, using adult volume-cycled ventilators in the mid-1970s, often resulted in severe air leak, chronic lung disease, and death. Although volume-targeted modes have evolved to allow pre-set tidal volumes as small as 2 mL, there are still questions regarding the accuracy and precision of these modes when large endotracheal tube leaks are present and following large changes in lung mechanics. Further, some of these modes are cumbersome to operate, causing clinicians to resort to PCV mode to support their patients.

Aside from PCV and volume-targeted ventilator approaches, another major controversy involves choosing between conventional ventilation and HFOV as the initial strategy in pre-term infants. A recent Cochrane review stated: "There is no clear evidence that elective HFOV offers important advantages over conventional ventilation when used as the initial ventilation strategy to treat pre-term infants with acute pulmonary dysfunction."⁵⁰ In 2010, a systematic review and meta-analysis,⁵¹ using individual patient data, from 12 randomized controlled trials ($n = 3,229$ patients) compared outcomes in pre-term infants using HFOV versus gentle conventional ventilation. There were no observed differences in chronic lung disease, mortality, or neurological insult. However, when randomization occurred earlier (1–4 h), HFOV showed a benefit in reduced death and chronic lung disease over conventional ventilation ($P = .01$). HFOV was associated with an increase in air leaks and a reduction in surgical ligation of patent ductus arteriosus or retinopathy of prematurity (stage 2 or more). Many of these studies were conducted prior to the widespread use of surfactant, antenatal steroids, permissive hypercapnia, and volume-targeted strategies. Further, there is a lack of description of ventilator approaches in the gentle-ventilation group. Nonetheless, HFOV and conventional ventilation appear to be equally effective. In the future, clinical studies comparing early HFOV to volume-targeted ventilation and PCV may be useful.

Inhaled Nitric Oxide

Inhaled nitric oxide is approved by the United States Food and Drug Administration for the treatment of term and near-term neonates with hypoxemic respiratory failure associated with clinical or echocardiographic evidence of pulmonary arterial hypertension. DiBlasi et al⁵² conducted a systematic review of the literature with the intention of making recommendations related to the clinical use of inhaled nitric oxide for its Food and Drug Administration approved indication. Using the Grading of Recommenda-

tions Assessment, Development, and Evaluation (GRADE) scoring system, 22 recommendations were developed for the use of inhaled nitric oxide in newborns, which should be useful for clinicians, for the labeled indication.

Aerosol Therapy

A number of papers published each year cover a variety of pharmacologic agents routinely used by respiratory clinicians. A search of the PubMed database including the terms aerosol therapy for 2010 limited to English language and humans resulted in 691 references. Only 25% (175) of these referred to clinical trials, and 141 were randomized comparisons. To cover some of the most common drugs that affect outcomes for diseases such as asthma, bronchiolitis, COPD, and CF, only 26 selected randomized clinical trials were included in this review. A myriad of pharmacologic agents that affect the respiratory system are investigated almost every day in laboratories and in the clinical setting. As challenging as it may sound, it is critical to the RT to gain a good understanding of the different drug categories, old and new, that affect the management of patients with respiratory disease.

Short-Acting β -Adrenergic Agents

Whether age range and aerosol device influence plasma concentration of albuterol in the acute care setting are questions often asked by clinicians. A randomized clinical trial was conducted in 46 children between ages 1 and 5 years with a diagnosis of acute asthma crisis.⁵³ There were 25 children who received albuterol from pressurized metered-dose inhaler with spacer (50 $\mu\text{g/kg}$), and 21 children received albuterol via nebulization (150 $\mu\text{g/kg}$), 3 times during a 1-hour period. Albuterol plasma concentration was compared in patients ≤ 2 years and > 2 years of age. While no differences were seen between the 2 aerosol delivery systems, significantly higher plasma albuterol was found in patients ≤ 2 years old.

Albuterol delivered from pressurized metered-dose inhaler is often administered to infants with acute obstructive airway disease. However, the safety of higher than regular doses is always of concern. A study of hydrofluoroalkane (HFA) propelled albuterol 180 μg ($n = 43$) or 360 μg ($n = 44$) administered from a pressurized metered-dose inhaler with a valved holding chamber and face mask, in an urgent-care setting, reported that cumulative dosing with the HFA propelled albuterol from the metered-dose inhaler with spacer and face mask in children younger than 2 years did not result in any important safety issues and improved Modified Tal Asthma Symptoms Score by at least 48%.⁵⁴

Long-Acting β -Adrenergic Agents

Indacaterol, the first once-daily administered long-acting β -adrenergic (LABA), was studied in patients with COPD by Donohue et al.⁵⁵ In this study, 1,683 patients with moderate-to-severe COPD were randomized to double-blind indacaterol 150 μg or 300 μg , or placebo, or open-label tiotropium 18 μg , all once daily, for 26 weeks, to compare their efficacy. Trough FEV₁ at week 12 was higher with indacaterol than with tiotropium. At week 26, total dyspnea index and the Saint George Respiratory Questionnaire score with indacaterol doses were better than with tiotropium. The incidence of adverse events was similar across treatments.

Sleep-disordered breathing with hypoxemia and hypercapnia is common in patients with moderate to severe COPD. The study by Ryan et al.⁵⁶ evaluated the effects of salmeterol on sleeping oxygen saturation (S_{pO_2}) and quality of sleep. They compared the effects of 4 weeks of treatment with salmeterol 50 μg twice daily and matching placebo in 12 patients. They found that while mean S_{pO_2} and the percentage of sleep spent below 90% of S_{pO_2} improved significantly with salmeterol, sleep quality was similar in both groups.

Safety and efficacy of arformoterol and formoterol in subjects with COPD were evaluated in a multicenter, 6-month randomized double-blind double-dummy trial.⁵⁷ Subjects were randomized to receive either nebulized arformoterol 15 μg ($n = 149$), 25 μg ($n = 147$), or racemic formoterol 12 μg ($n = 147$) delivered via dry-powder inhaler (DPI) twice daily. Both arformoterol and formoterol were well tolerated, and their use was associated with improvement in pulmonary function and health status in subjects with COPD, with no apparent development of tolerance.

Long-Acting Antimuscarinic Agents

The only Food and Drug Administration currently approved long-acting antimuscarinic is tiotropium bromide, which is administered via a DPI as maintenance therapy to patients with moderate to severe COPD. Alternative devices of administration for tiotropium, such as the Respimat Soft Mist Inhaler, have been evaluated. A very recent study by Rau-Berger et al.⁵⁸ reported that, in patients with COPD, receiving tiotropium via Respimat Soft Mist Inhaler 5 μg once daily, physical function improved rapidly within 6 weeks of treatment, irrespective of smoking status. Adverse events were reported by 4.0% of patients. Similarly, its efficacy and safety at doses of 5 μg or 10 μg via the Respimat Soft Mist Inhaler versus placebo have been recently evaluated in 1,990 patients with COPD by Bateman et al.⁵⁹ Tiotropium Respimat Soft Mist Inhaler 5 μg and 10 μg were associated with sustained improve-

ments in FEV₁, health-related quality of life and Mahler Transition Dyspnea Index (total dyspnea index), and a lower COPD exacerbation rate. Patients who received the 10- μg dose reported a higher frequency of anticholinergic adverse events. When compared to the traditional 18 μg via Handihaler in 134 patients with COPD, Ichinose et al found that both formulations showed a similar profile of efficacy, safety, and pharmacokinetics.⁶⁰

Inhaled Corticosteroid Therapy

Although there is sufficient evidence to support the association between the use of oral corticosteroids and the decrease in the bone mineral density in children, there is still a controversy about the risk associated to the use of inhaled corticosteroids (ICS). Turpeinen et al⁶¹ measured the bone mineral density of the lumbar vertebrae before and after an 18-month treatment with budesonide on 136 children, 5–10 years old, with newly detected persistent asthma. When compared to children treated with disodium cromoglycate, regular budesonide treatment resulted in a significantly smaller increase in bone mineral density ($P = .02$) and height ($P = .001$).

Another unwanted side effect of oral corticosteroids administration is the inhibition of the hypothalamic-pituitary-adrenal axis. However, ICS at a medium-to-high dose range may also affect the hypothalamic-pituitary-adrenal axis. Kosoglou et al⁶² recently found that mometasone DPI 400 μg administered once daily in the evening did not suppress the hypothalamic-pituitary-adrenal axis, as cortisol levels did not change significantly, in a group of non-smoking adults ages 18–50 years with mild-to-moderate asthma.

Once-daily administration of drugs simplifies scheduling for patients receiving multiple medications and improves adherence and compliance, which are critical to positive clinical outcomes. An evaluation of adherence with mometasone furoate DPI 400 μg once-daily in the evening versus 200 μg twice-daily dosing in 1,233 patients ≥ 12 years old with mild-to-moderate persistent asthma, by Price et al,⁶³ revealed that after 12 weeks, mean adherence rates were significantly better with the once-daily administration ($P < .001$).

Phosphodiesterase Inhibitors

Phosphodiesterase 4 (PDE4) has become an important molecular target for the development of novel therapies for asthma and COPD. PDE4 inhibitors may modify airway obstruction, airway inflammation, and airway remodeling and hyper-reactivity. However, they may elicit severe gastrointestinal side effects. Evaluation of a new inhaled PDE4, GSK256066, on 24 steroid-naïve atopic asthmatics with both early and late responses to inhaled

allergen was associated with a significantly reduced late and early allergic reactions, compared to placebo. There was no effect on pre-allergen FEV₁ or methacholine reactivity post-allergen. GSK256066 was well tolerated, with low systemic exposure. This is the first inhaled PDE4 inhibitor to show therapeutic potential in asthma that is well tolerated, with low systemic exposure.⁶⁴

Long-Acting β -Adrenergic Plus Inhaled Corticosteroid

Combination of a long-acting bronchodilator and ICS has been shown to be more effective than monotherapy in the stepwise approach to managing patients with obstructive airway disease. The most recommended dose schedule is twice daily, due to the well known pharmacokinetics of long-acting β -adrenergic agents. Berger et al⁶⁵ evaluated whether or not the combination budesonide/formoterol (BUD/FOR) once-daily was as effective as twice-daily dosing in patients age ≥ 16 y with mild to moderate asthma. This large multicenter study ($n = 752$) showed that twice-daily BUD/FOR (320/18 μg daily) was more effective than BUD/FOR once daily (160/9 μg daily) when evaluated for evening pulmonary function assessments and daytime rescue medication use ($P \leq .05$). Administration of formoterol has been successfully used for fast relief of bronchospasm symptoms in addition to its use as maintenance therapy.

Aalbers et al⁶⁶ compared the protective effect of BUD/FOR with formoterol, albuterol, and placebo on repeated provocations with inhaled adenosine monophosphate in 17 patients with asthma. They found that a single dose of BUD/FOR provided a greater protective effect against inhaled adenosine-monophosphate-induced bronchoconstriction than formoterol alone.

When BUD/FOR was compared to salmeterol/fluticasone for the management of 2,866 patients age ≥ 16 years with persistent asthma by Kuna,⁶⁷ he found that administration of BUD/FOR for both maintenance and reliever therapy prolonged time to first severe exacerbation, when compared to BUD/FOR (320/9 μg daily) and salmeterol/fluticasone (500/100 μg daily) fixed maintenance dose ($P = .04$ and $P = .009$, respectively). Compared with salmeterol/fluticasone fixed maintenance-dose treatment, BUD/FOR (640/18 μg daily) was associated with a reduced risk of hospitalizations/ED visits by 28% (relative rate [RR] 0.72, 95% CI 0.53–0.98, $P = .03$) and BUD/FOR maintenance and reliever therapy by 37% (RR 0.63, 95% CI 0.46–0.87, $P = .004$).

In a study of 30 patients with asthma, the effects of salmeterol/fluticasone were compared to a combination of extra-fine inhaled beclomethasone/formoterol (BDP/FOR) on both large and small airways.⁶⁸ After a 1–4-week run-in period, and a 12-week treatment it was found that while

there was a significant but similar increase ($P < .01$) versus baseline observed in pre-dose FEV₁ in both BDP/FOR and salmeterol/fluticasone groups, only those patients in the BDP/FOR group had a significant improvement in the provocation dose required to produce a 20% FEV₁ decrease ($P = .01$). No differences were recorded in single-breath nitrogen test parameters.

The most recent Cochrane meta-analysis evaluated the addition of LABA agents to ICS versus higher dose ICS in adults and children with persistent asthma.⁶⁹ The results suggest that combination of LABA and ICS is modestly more effective in reducing the risk of exacerbation requiring oral corticosteroid than a higher dose of ICS. While modest improvement in lung function, symptoms, and use of rescue short-acting β -adrenergic agents was also observed in adolescents and adults, combination therapy appeared to be associated with modest improvement and increased risk of oral-corticosteroids-treated exacerbations and hospital admissions in children under the age of 12 years.

Long-Acting Antimuscarinic Plus Inhaled Corticosteroid

While traditionally LABA therapy improves symptoms in patients whose asthma is poorly controlled by an ICS alone, alternative treatments for adults with uncontrolled asthma have been explored. A trial involving 210 patients with asthma evaluated if long-acting antimuscarinic therapy improved symptoms in patients whose asthma was poorly controlled by an ICS alone.⁷⁰ Tiotropium bromide was added to ICS, as compared with a doubling of the dose of the ICS or the addition of the LABA salmeterol. The use of tiotropium was associated with a significantly higher morning peak expiratory flow, evening peak expiratory flow, proportion of asthma control days, FEV₁ before bronchodilation, and daily symptom scores, as compared with a doubling of the dose of an ICS. Its effects appeared to be equivalent to those with the addition of salmeterol.

Nebulized Hypertonic Saline

Nebulized hypertonic saline solution is frequently used in patients with cystic fibrosis (CF) in order to enhance mucociliary clearance. The efficacy and safety of nebulized 3% saline and albuterol in the treatment of 93 infants with mild to moderate bronchiolitis was compared with the administration of albuterol dissolved in 0.9% saline. Both therapies were administered 3 times daily until discharge. Luo et al⁷¹ reported that nebulized 3% saline was associated with a significantly shorter time for wheezing remission, cough remission, moist crackles disappearance, and average stay. When 3% saline was compared to nebulized 5% saline or 0.9% saline for treating acute bron-

chiolitis in 165 infants age < 18 months in the pre-hospital setting, after 48 hours of therapy, the mean severity score for the 5% saline group was 3.6 ± 1.09 , and that for the 0.9% saline group was 4.12 ± 1.11 ($P = .04$).⁷² The mean severity score for the 3% saline group was intermediate at 4.00 ± 1.22 . No adverse reactions or other safety concerns were identified on the previous 2 reports. While several studies report differences between hypertonic saline and 0.9% saline, a study by Anil et al⁷³ that investigated the effectiveness of nebulized albuterol, epinephrine, 3% saline, and 0.9% saline in 186 small children with mild bronchiolitis, found no significant differences between groups.

In regards to CF, Amin et al⁷⁴ evaluated the effects of 4 weeks of 7% saline compared to 0.9% saline on lung clearance index, a measure of ventilation inhomogeneity, of 20 patients. Twice-daily 7% hypertonic saline inhalation significantly improved the lung clearance index compared with 0.9% saline.

Inhaled Mannitol

Inhaled mannitol appears to improve mucus clearance due to its osmotic characteristics. In order to evaluate the changes in the physical properties associated with mannitol, Daviskas et al⁷⁵ investigated sputum after a 2-week treatment in patients with CF. Inhaled mannitol was associated with a reduction of solids, a significant reduction in surface tension, and contact angle. These effects were sustained and correlated with positive airway function changes.

Adi et al⁷⁶ assessed the potential of delivering a combination containing mannitol and ciprofloxacin (a fluoroquinolone), as a DPI formulation for inhalation. They found that mannitol did not appear to alter the effectiveness of the ciprofloxacin antimicrobial activity. Therefore, combination of co-spray-dried mannitol and ciprofloxacin from a DPI may become an attractive alternative to promote mucus clearance while treating infection in patients with chronic respiratory infections such as COPD and CF.

Inhaled Antibiotic Therapy

Inhaled antibiotics have become a critical component of the management of patients with CF, as it considerably decreases the side effects associated with their systemic administration. Noah et al⁷⁷ found that in 15 clinically stable children with CF and infection with *Pseudomonas*, 2 weeks of systemic antibiotics resulted in greater short-term reduction in lower airways inflammation than 4 weeks of inhaled tobramycin. Evaluation of new inhaled antibiotics and new methods of delivery has resulted in more alternatives for patients with respiratory infections.

Luyt et al⁷⁸ evaluated the pharmacokinetics and lung delivery of nebulized amikacin administered via a vi-

brating-mesh nebulizer for 7–14 days in 28 intubated patients with Gram-negative ventilator-associated pneumonia. They found that delivery of nebulized amikacin via vibrating-mesh technology achieved very high aminoglycoside concentration in the respiratory epithelium exceeding the typical levels required to manage Gram-negative microorganisms.

Summary

In this paper we reviewed the important recent literature related to respiratory care in the topic areas of invasive mechanical ventilation, NIV, pediatric mechanical ventilation, and aerosol therapy. It is our hope that this will help to familiarize the reader with the important literature in these subject areas.

REFERENCES

1. Rubin BK, Dhand R, Ruppel GL, Branson RD, Hess DR. Respiratory care year in review 2010. Part 1: asthma, chronic obstructive pulmonary disease, pulmonary function testing, ventilator-associated pneumonia. *Respir Care* 2011;56(4):488-502.
2. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld D, Thompson BT; National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004;22:351(4):327-336.
3. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, et al; Lung Open Ventilation Study Investigators. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008;299(6):637-645.
4. Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, et al; Expiratory Pressure (Express) Study Group. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008;299(6):646-655.
5. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA* 2010;303(9):865-873.
6. Myers TR, MacIntyre NR. Respiratory controversies in the critical care setting. Does airway pressure release ventilation offer important new advantages in mechanical ventilator support? *Respir Care* 2007;52(4):452-460.
7. Maxwell RA, Green JM, Waldrop J, Dart BW, Smith PW, Brooks D, et al. A randomized prospective trial of airway pressure release ventilation and low tidal volume ventilation in adult trauma patients with acute respiratory failure. *J Trauma* 2010;69(3):501-510.
8. González M, Arroliga AC, Frutos-Vivar F, Raymonds K, Esteban A, Putensen C, et al. Airway pressure release ventilation versus assist-control ventilation: a comparative propensity score and international cohort study. *Int Care Med* 2010;36(5):817-827.
9. Sud S, Sud M, Friedrich JO, Meade MO, Ferguson ND, Wunsch H, Adhikari NK. High frequency oscillation in patients with acute lung injury and acute respiratory distress syndrome (ARDS): systematic review and meta-analysis. *BMJ* 2010;340:c2327.

10. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342(18):1301-1308.
11. Chung KK, Wolf SE, Renz EM, Allan PF, Aden JK, Merrill GA, et al. High frequency percussive ventilation and low tidal volume ventilation in burns: a randomized controlled trial. *Crit Care Med* 2010; 38(10):1970-1977.
12. Allan PF. High-frequency percussive ventilation: pneumotachograph validation and tidal volume analysis. *Respir Care* 2010;55(6):734-740.
13. Short K, Bougataf A, Khushid F, Kenney BD, Miller K. High-frequency percussive ventilation (letter). *Respir Care* 2010;55(12):1762-1764;author reply:1764-1767.
14. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loun-dou A, et al. ACURASYS Study Investigators. Neuromuscular block-ers in early acute respiratory distress syndrome. *N Engl J Med* 2010; 363(12):1107-1116.
15. Dreher M, Kabitz HJ, Burgardt V, Walterspercher S, Windisch W. Proportional assist ventilation improves exercise capacity in patients with obesity. *Respiration* 2010;80(2):106-111.
16. Moderno EV, Yamaguti WP, Schettino GP, Kairalla RA, Martins MA, Carvalho CR. Effects of proportional assisted ventilation on exercise performance in idiopathic pulmonary fibrosis patients. *Respir Med* 2010;104(1):134-141.
17. Coisel Y, Chanques G, Jung B, Constantin JM, Capdevila X, Matecki S, et al. Neurally adjusted ventilatory assist in critically ill post-operative patients: a crossover randomized study. *Anesthesiology* 2010;113(4):925-935.
18. Terzi N, Pelieu I, Guittet L, Ramakers M, Seguin A, Daubin C, et al. Neurally adjusted ventilatory assist in patients recovering spontane-ous breathing after acute respiratory distress syndrome: physiologi-cal evaluation. *Crit Care Med* 2010;38(9):1830-1837.
19. Bengtsson JA, Edberg KE. Neurally adjusted ventilatory assist in children: an observational study. *Pediatr Crit Care Med* 2010;11(2): 253-257.
20. Pierson DJ. Patient-ventilator interaction. *Respir Care* 2011;56(2): 214-228.
21. Bierer GB, Soo Hoo GW. Noninvasive ventilation for acute respi-ratory failure: a national survey of veterans affairs hospitals. *Respir Care* 2009;54(10):1313-1320.
22. Hess DR, Pang JM, Camargo CA. A survey of the use of noninvasive ventilation in academic emergency departments in the United States. *Respir Care* 2009;54(10):1306-1312.
23. Crimi C, Noto A, Princi P, Esquinas A, Nava S. A European survey of noninvasive ventilation practice. *Eur Respir J* 2010;36(2):362-369.
24. Epstein SK, Ciubotaru RL, Wong JB. Effect of failed extubation on the outcome of mechanical ventilation. *Chest* 1997;112(1):186-192.
25. Epstein SK, Ciubotaru RL. Independent effects of etiology of failure and time to reintubation on outcome for patients failing extubation. *Am J Respir Crit Care Med* 1998;158(2):489-493.
26. Ferrer M, Sellarés J, Valencia M, Carrillo A, Gonzalez G, Badia JR, et al. Non-invasive ventilation after extubation in hypercapnic pa-tients with chronic respiratory disorders: randomised controlled trial. *Lancet* 2009;374(9695):1082-1088.
27. Boeken U, Schurr P, Kurt M, Feindt P, Lichtenberg A. Early rein-tubation after cardiac operations: impact of nasal continuous positive airway pressure (nCPAP) and noninvasive positive pressure veni-lation (NPPV). *Thorac Cardiovasc Surg* 2010;58(7):398-402.
28. Nin N, Soto L, Hurtado J, Lorente JA, Buroni M, Arancibia F, et al. *J Crit Care* 2010. DOI:10.1016/j.jcrrc.2010.05.031.
29. Conti G, Larsson A, Nava S, Navalesi P. On the role of noninvasive ventilation to treat patients during H1N1 pandemic. October 2009. http://www.ersnet.org/images/stories/pdf/on_the_role_of_non-invasive_ventilation_niv_to_treat_patients_during_the_h1n1_influenza.pdf. Ac-cessed February 7, 2011.
30. McCracken. The consequences of withholding noninvasive venti-lation during an epidemic (letter). *Respir Care* 2009;54(10):1412-1413.
31. Pediatric Acute Lung Injury and Sepsis Investigators. http://pedsccm.org/palisi_network.php. Accessed February 7, 2011.
32. Vermont Oxford Network. <http://www.vtoxford.org>. Accessed Feb-ruary 7, 2011.
33. National Institute of Health, Eunice Kennedy Shriver National In-stitute of Child Health and Human Development. <http://www.nichd.nih.gov>. Accessed February 7, 2011.
34. Aly H. Ventilation without tracheal intubation. *Pediatrics* 2009; 124(2):786-789.
35. Avery ME, Tooley WH, Keller JB, Hurd SS, Bryan MH, Cotton RB, et al. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. *Pediatrics* 1987;79(1):26-30.
36. Lista G, Fontana P, Castoldi F, Caviglioli F, Dani C. Does sustained lung inflation at birth improve outcome of preterm infants at risk for respiratory distress syndrome? *Neonatology* 2011;99(1):45-50.
37. Lindner W, Högel J, Pohlandt F. Sustained pressure-controlled in-flation or intermittent mandatory ventilation in preterm infants in the delivery room? A randomized, controlled trial on initial respiratory support via nasopharyngeal tube. *Acta Paediatr* 2005;94(3):303-309.
38. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network; Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, Laptook AR, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med* 2010;362(21):1970-1979. Erratum in: *N Engl J Med* 2010;362(23):2235.
39. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network; Carlo WA, Finer NN, Walsh MC, Rich W, Gantz MG, Laptook AR, et al. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med* 2010;362(21):1959-1969.
40. Sandri F, Plavka R, Ancora G, Simeoni U, Stranak Z, Martinelli S, et al; CURPAP Study Group. Prophylactic or early selective surfac-tant combined with nCPAP in very preterm infants. *Pediatrics* 2010; 125(6):e1402-e1409.
41. Courtney SE, Kahn DJ, Singh R, Habib RH. Bubble and ventilator-derived nasal continuous positive airway pressure in premature in-fants: work of breathing and gas exchange. *J Perinatol* 2011;31(1): 44-50.
42. Pillow JJ, Travadi JN. Bubble CPAP: is the noise important? An in vitro study. *Pediatr Res* 2005;57(6):826-830.
43. Pillow JJ, Hillman N, Moss TJ, Polglase G, Bold G, Beaumont C, et al. Bubble continuous positive airway pressure enhances lung vol-ume and gas exchange in preterm lambs. *Respir Crit Care Med* 2007;176(1):63-69.
44. DiBlasi RM, Zignego JC, Smith CV, Hansen TN, Richardson CP. Effective gas exchange in paralyzed juvenile rabbits using simple, inexpensive respiratory support devices. *Pediatr Res* 2010;[Epub ahead of print]
45. DiBlasi RM, Zignego JC, Tang DM, Hildebrandt J, Smith CV, Han-sen TN, Richardson CP. Noninvasive respiratory support of juvenile rabbits by high-amplitude bubble continuous positive airway pres-sure. *Pediatr Res* 2010;67(6):624-629.
46. Ancora G, Maranella E, Grandi S, Pierantoni L, Guglielmi M, Fal-della G. Role of bilevel positive airway pressure in the management of preterm newborns who have received surfactant. *Acta Paediatr* 2010;99(12):1807-1811.
47. Lista G, Castoldi F, Fontana P, Daniele I, Caviglioli F, Rossi S, et al. Nasal continuous positive airway pressure (CPAP) versus bi-level nasal CPAP in preterm babies with respiratory distress syndrome: a

- randomized control trial. *Arch Dis Child Fetal Neonatal Ed* 2010; 95(2):F85-F89.
48. van Kaam AH, Rimensberger PC, Borensztajn D, De Jaegere AP. Neovent Study Group. Ventilation practices in the neonatal intensive care unit: a cross-sectional study. *J Pediatr* 2010;157(5):767-771.
49. Wheeler K, Klingenberg C, McCallion N, Morley CJ, Davis PG. Volume-targeted versus pressure-limited ventilation in the neonate. *Cochrane Database Syst Rev* 2010;(11):CD003666.
50. Cools F, Henderson-Smart DJ, Offringa M, Askie LM. Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. *Cochrane Database Syst Rev* 2009;(3):CD000104.
51. Cools F, Askie LM, Offringa M, Asselin JM, Calvert SA, Courtney SE, et al. PreVILIG collaboration. Elective high-frequency oscillatory versus conventional ventilation in preterm infants: a systematic review and meta-analysis of individual patients' data. *Lancet* 2010; 375(9731):2082-2091.
52. DiBlasi RM, Myers TR, Hess DR; American Association for Respiratory Care. Evidence-based clinical practice guideline: inhaled nitric oxide for neonates with acute hypoxic respiratory failure. *Respir Care* 2010;55(12):1717-1745.
53. Rotta ET, Amantéa SL, Froehlich PE, Becker A. Plasma concentrations of salbutamol in the treatment of acute asthma in a pediatric emergency. Could age be a parameter of influence? *Eur J Clin Pharmacol* 2010;66(6):605-610.
54. Kaashmiri M, Shepard J, Goodman B, Lincourt WR, Trivedi R, Ellsworth A, Davis AM. Repeat dosing of albuterol via metered-dose inhaler in infants with acute obstructive airway disease: a randomized controlled safety trial. *Pediatr Emerg Care* 2010;26(3):197-202.
55. Donohue JF, Fogarty C, Lötvall J, Mahler DA, Worth H, Yorgancioglu A, et al. INHANCE Study Investigators. Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. *Am J Respir Crit Care Med* 2010;182(2):155-162.
56. Ryan S, Doherty LS, Rock C, Nolan GM, McNicholas WT. Effects of salmeterol on sleeping oxygen saturation in chronic obstructive pulmonary disease. *Respiration* 2010;79(6):475-481.
57. Hanania NA, Donohue JF, Nelson H, Sciarappa K, Goodwin E, Baumgartner RA, Hanrahan JP. The safety and efficacy of arformoterol and formoterol in COPD. *COPD* 2010;7(1):17-31.
58. Rau-Berger H, Mitfessel H, Glaab T. Tiotropium Respimat improves physical functioning in chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2010;5:367-373.
59. Bateman E, Singh D, Smith D, Disse B, Towse L, Massey D, et al. Efficacy and safety of tiotropium Respimat SMI in COPD in two 1-year randomized studies. *Int J Chron Obstruct Pulmon Dis* 2010; 5:197-208.
60. Ichinose M, Fujimoto T, Fukuchi Y. Tiotropium 5 µg via Respimat and 18 µg via HandiHaler; efficacy and safety in Japanese COPD patients. *Respir Med* 2010;104(2):228-236.
61. Turpeinen M, Pelkonen AS, Nikander K, Sorva R, Selroos O, Juntunen-Backman K, Haahela T. Bone mineral density in children treated with daily or periodical inhaled budesonide: the Helsinki Early Intervention Childhood Asthma study. *Pediatr Res* 2010;68(2): 169-173.
62. Kosoglou T, Cutler DL, Staudinger H, Herron JM. Once-daily evening dosing of mometasone furoate administered via a dry powder inhaler does not adversely affect the hypothalamic-pituitary-adrenal axis. *Chest* 2010;137(1):115-121.
63. Price D, Robertson A, Bullen K, Rand C, Horne R, Staudinger H. Improved adherence with once-daily versus twice-daily dosing of mometasone furoate administered via a dry powder inhaler: a randomized open-label study. *BMC Pulm Med* 2010;10:1.
64. Singh D, Petavy F, Macdonald AJ, Lazaar AL, O'Connor BJ. The inhaled phosphodiesterase 4 inhibitor GSK256066 reduces allergen challenge responses in asthma. *Respir Res* 2010;11:26.
65. Berger WE, Bleecker ER, O'Dowd L, Miller CJ, Mezzanotte W. Efficacy and safety of budesonide/formoterol pressurized metered-dose inhaler: randomized controlled trial comparing once- and twice-daily dosing in patients with asthma. *Allergy Asthma Proc* 2010;(1): 49-59.
66. Aalbers R, Boersma M, van der Woude HJ, Jonkers RE. Protective effect of budesonide/formoterol compared with formoterol, salbutamol and placebo on repeated provocations with inhaled AMP in patients with asthma: a randomised, double-blind, cross-over study. *Respir Res* 2010;11:66.
67. Kuna P. Treatment comparison of budesonide/formoterol with salmeterol/fluticasone propionate in adults aged >16 years with asthma: post hoc analysis of a randomized, double-blind study. *Clin Drug Investig* 2010;30(9):565-579.
68. Scichilone N, Battaglia S, Sorino C, Paglino G, Martino L, Paternò A, et al. Effects of extra-fine inhaled beclomethasone/formoterol on both large and small airways in asthma. *Allergy* 2010;65(7):897-902.
69. Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting β₂-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2010;(5):CD005535.
70. Peters SP, Kunselman SJ, Icitovic N, Moore WC, Pascual R, Amended BT, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *N Engl J Med* 2010;363(18):1715-1726.
71. Luo Z, Liu E, Luo J, Li S, Zeng F, Yang X, Fu Z. Nebulized hypertonic saline/salbutamol solution treatment in hospitalized children with mild to moderate bronchiolitis. *Pediatr Int* 2010;52(2):199-202.
72. Al-Ansari K, Sakran M, Davidson BL, El Sayyed R, Mahjoub H, Ibrahim K. Nebulized 5% or 3% hypertonic or 0.9% saline for treating acute bronchiolitis in infants. *J Pediatr* 2010;157(4):630-634.
73. Anil AB, Anil M, Saglam AB, Cetin N, Bal A, Aksu N. High volume normal saline alone is as effective as nebulized salbutamol-normal saline, epinephrine-normal saline, and 3% saline in mild bronchiolitis. *Pediatr Pulmonol* 2010;45(1):41-47.
74. Amin R, Subbarao P, Jabar A, Balkovec S, Jensen R, Kerrigan S, et al. Hypertonic saline improves the LCI in paediatric patients with CF with normal lung function. *Thorax* 2010;65(5):379-383.
75. Daviskas E, Anderson SD, Jaques A, Charlton B. Inhaled mannitol improves the hydration and surface properties of sputum in patients with cystic fibrosis. *Chest* 2010;137(4):861-868.
76. Adi H, Young PM, Chan HK, Agus H, Traini D. Co-spray-dried mannitol-ciprofloxacin dry powder inhaler formulation for cystic fibrosis and chronic obstructive pulmonary disease. *Eur J Pharm Sci* 2010;40(3):239-247.
77. Noah TL, Ivins SS, Abode KA, Stewart PW, Michelson PH, Harris WT, et al. Inhaled versus systemic antibiotics and airway inflammation in children with cystic fibrosis and *Pseudomonas*. *Pediatr Pulmonol* 2010;45(3):281-290.
78. Luyt CE, Clavel M, Guntupalli K, Johannigman J, Kennedy JJ, Wood C, et al. Pharmacokinetics and lung delivery of PDDS-aerosolized amikacin (NKTR-061) in intubated and mechanically ventilated patients with nosocomial pneumonia. *Crit Care* 2009;13(6):R200.