Respiratory Care Year in Review 2012: Invasive Mechanical Ventilation, Noninvasive Ventilation, and Cystic Fibrosis

Richard H Kallet MSc RRT FAARC, Teresa A Volsko MHHS RRT FAARC, and Dean R Hess PhD RRT FAARC

For the busy clinician, educator, or manager, it is becoming an increasing challenge to filter the literature to what is relevant to one's practice and then update one's practice based on the current evidence. The purpose of this paper is to review the recent literature related to invasive mechanical ventilation, noninvasive ventilation, and cystic fibrosis. These topics were chosen and reviewed in a manner that is most likely to have interest to the readers of RESPIRATORY CARE. *Key words: cystic fibrosis; mechanical ventilation; noninvasive ventilation; respiratory failure.* [Respir Care 2013;58(4): 702–711. © 2013 Daedalus Enterprises]

Introduction

For the busy clinician, educator, or manager it is a challenge to review the literature relevant to one's practice and then update that practice based on the current evidence. At the American Association for Respiratory Care Congress 2012, RESPIRATORY CARE presented a series of lectures on the theme of "Year in Review." As done twice before,[1-3] topics were chosen that are likely to have special interest

Mr Kallet is affiliated with Respiratory Care Services, Department of Anesthesia, University of California, San Francisco at San Francisco General Hospital, San Francisco, California. Ms Volsko is affiliated with the Respiratory Care Department, Akron Children's Hospital, Akron, Ohio. Dr Hess is affiliated with Respiratory Care Services, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.

Dr Hess has disclosed relationships with Philips Respironics, ResMed, Breathe Technologies, Pari, Covidien, and Maquet. The other authors have disclosed no conflicts of interest.

The authors presented a version of this paper at the AARC Congress 2012, held November 10–13, in New Orleans, Louisiana.

Correspondence: Dean R Hess PhD RRT FAARC, Respiratory Care Services, Ellison 401, Massachusetts General Hospital, 55 Fruit Street, Boston MA 02114. E-mail: dhess@partners.org.

DOI: 10.4187/respcare.02412

to the readers of RESPIRATORY CARE. In this paper we review topics related to invasive mechanical ventilation, noninvasive ventilation, and cystic fibrosis (CF).

Invasive Mechanical Ventilation

The more interesting papers on invasive mechanical ventilation published in 2012 addressed the effects of lung-protective ventilation (LPV) on long-term (ie, 24 months) mortality in patients with ARDS,[4] using physiologic dead-space-to-tidal-volume ratio (V_D/V_T) to set PEEP in patients with ARDS,[5] the utility of monitoring diaphragmatic electromyography during spontaneous breathing trials (SBTs) to predict extubation outcomes,[6] and a systematic review on the impact of unplanned extubation on patient outcomes.[7]

Tidal Volume and 2-Year Mortality in ARDS

Since the landmark study by the National Institutes of Health ARDS Network[8] demonstrated that LPV reduces hospital mortality, there has been increased interest in longer-term outcomes. However, these studies have focused primarily on neurocognitive, neuromuscular, and other sequelae, rather than mortality.[9] In a large, prospective, 3-year observational study, Needham and colleagues tracked 485 patients with ARDS at 4 academic hospitals in the Baltimore, Maryland, area.[4] During hospitalization, end-inspiratory plateau pressure (P_{plat}) and V_T were collected twice daily and evaluated for adherence to established ARDS Network goals ($\leq$ 30 cm H_2O and $\leq$ 6.5 mL/kg predicted body weight, respectively).

With a mechanical ventilation duration median of 9 days, there were over 6,200 P_{plat} and V_T data points eligible for analysis (median of 8 per patient). It was disappointing that, in major academic medical centers highly experienced in LPV, only 41% of data met ARDS Network management goals. Among these patients, the majority (86%) met P_{plat} and V_T goals $<$ 50% of the time. Overall, 37% of patients with ARDS never achieved the P_{plat} and V_T goals.

Overall mortality increased from 44% at 30 days after ARDS diagnosis to 64% at 24 months, with most deaths (62%) occurring within the first 12 months. As would be anticipated, age, comorbidities, organ failure scores, and cumulative fluid balance were all independently associated with mortality. However, patients who were managed with strict adherence to ARDS Network goals had an absolute 24-month mortality risk-reduction of 7.8%. Even patients whose P_{plat} and V_T achieved ARDS Network goals only 50% of the time had a mortality benefit at 24 months (4% risk reduction). In addition, there appeared to be a linear relationship between V_T and mortality, with an 18% relative increase in mortality for every 1 mL/kg above 6.5 mL/kg. Furthermore, even modest discrepancies in V_T that were within an acceptable range for LPV (6.6–8.5 mL/kg) were associated with an adjusted hazard ratio of 1.59 for mortality risk that increased further to 1.97 in patients managed with a $V_T > 8.5$ mL/kg. The findings reported by Needham and colleagues[4] were similar to a recent smaller European study where overall mortality in patients with ARDS at 12 months was 60%.[10]

The study by Needham and colleagues[4] underscores the previous findings that LPV has not yet been applied systematically to patients with ARDS, even at centers with a high degree of experience with LPV.[11] Moreover, there is mounting evidence regarding the importance of limiting V_T to prevent ARDS in at-risk patients,[12] as well as preventing both ARDS and non-pulmonary organ damage in patients without known risk factors.[13,14] A more concerted effort in limiting V_T appears necessary if outcomes are to be optimized among critically ill patients undergoing mechanical ventilation.

PEEP Titration Guided by Dead-Space Measurements

The seminal work of Suter and colleagues[15] on optimal PEEP demonstrated that deterioration in both respiratory-system compliance (C_{RS}) and V_D/V_T are markers of lung over-distention, despite corresponding improvements in functional residual capacity (FRC) and arterial oxygenation. This was the first evidence from respiratory mechanics suggesting that ARDS is heterogeneous, which was reported a decade before confirmation by computed tomography studies.[16,17] Only recently, however, has V_D/V_T been utilized to guide PEEP titration by balancing lung recruitment against concurrent over-distention.[5,18,19]

The recent study by Guo and colleagues[5] incorporated C_{RS}, V_D/V_T, and FRC measurements into a PEEP-decrement method for determining optimal PEEP in patients with ARDS.[20] This small prospective study used a recruitment maneuver of 40 cm H_2O CPAP sustained for 30 seconds. Afterwards, PEEP was set initially at 20 cm H_2O, followed by 2 cm H_2O decrements to a final value of 0 cm H_2O. Consistent with previous studies,[18,19] they confirmed that the highest values for both FRC and P_{aO_2}/F_{IO_2} found at a PEEP of 20 cm H_2O were also associated with the lowest C_{RS} and highest V_D/V_T. During the decremental PEEP trial both FRC and P_{aO_2}/F_{IO_2} decreased while C_{RS} and V_D/V_T improved, although oxygenation and resting lung volume remained well above baseline values. More importantly, when PEEP was decreased below the nadir for V_D/V_T, there was a salient deterioration in P_{aO_2}/F_{IO_2} (24%) along with a mild increase in V_D/V_T, again suggestive of increasing intrapulmonary shunt from alveolar derecruitment.

The primary importance of this study is its suggestion of a safer, simplified approach to the recruitment maneuver/PEEP decremental trial,[20] wherein optimal PEEP is defined as the level just above the point that oxygen desaturation occurs. Therefore, it necessitates alveolar de-recruitment to identify optimal PEEP. In refractory ARDS (eg, severe H1N1 infection) any de-recruitment is potentially dangerous and may be avoided if PEEP titration is guided instead by dead-space measurements. In addition, V_D/V_T also was found to be the strongest predictor of mortality, compared to other measures such as lung injury score, FRC, and the Acute Physiology and Chronic Health Evaluation (APACHE II) score, which was consistent with the results of several previous studies.[21]

Breathing Pattern and Diaphragmatic Electromyography During an SBT

Neurally adjusted ventilatory assistance (NAVA) is a relatively new mode of closed-loop mechanical ventilation.[22] Although the added value of using NAVA in a typical mechanically ventilated patient is debatable, as it requires the placement of an esophageal probe, it may be useful in the subset of patients in whom the weaning process is prolonged and complicated. However, the technological intrigue surrounding diaphragmatic electrical activity (EAdi) in closed-loop ventilation detracts from a potentially more important feature: the ability to monitor and integrate the diaphragmatic electromyography with breathing pattern behavior in response to changing mechanical loads during weaning.

EAdi represents the intensity of diaphragmatic muscular contraction. Liu and colleagues[6] posed an elegant and practical question: does linking EAdi to a mechanical output such as spontaneous V_T during an SBT give useful information that may predict extubation readiness? They studied 52 patients who met basic weaning-readiness criteria and were first evaluated on pressure support ventilation (PSV) of 10 cm H_2O above a PEEP of 5 cm H_2O for 5 min. An SBT was then done for 30 min on CPAP of 5 cm H_2O, with data collected at 1, 5, 10, 15, and 30 min. Patients who passed the SBT using standard criteria underwent a trial of extubation. For study purposes failure was defined as the inability to pass the SBT, the need for noninvasive ventilatory support post-extubation, and reintubation or death within 48 hours following extubation. The SBT was successful in 67% of patients, who were extubated. However, an unusually large percentage (33%) failed the extubation trial within 48 hours, 59% of whom had COPD.

The most interesting finding was that breathing pattern within the first 5 min of the SBT was highly predictive of success or failure. Although the EAdi increased for all patients during this time, in those who failed extubation the EAdi increased to a level twice that found in those who were successfully extubated. When EAdi was expressed in terms of neuroventilatory efficiency (ie, spontaneous V_T relative to EAdi, or mL/μV), efficiency diminished in both groups during the SBT. However, the deterioration was much more severe in those who failed either the SBT or extubation trial. Using a cutoff of 25 mL/μV, neuroventilatory efficiency measured at 5 min into the SBT had the highest predictive value for successful extubation (area under the receiver operating characteristic curve 0.84, $P < .001$). The breathing pattern of patients who failed had a more pronounced and sustained drop in both minute ventilation and V_T, along with a rise in P_{aCO_2}. In other words, despite a very high degree of neuromuscular excitation, the diaphragm was unable to adapt to the increased work load. Monitoring EAdi may not be able to parse out the cause of failure (eg, intrinsic muscle fatigue, abnormal resting muscle geometry from hyperinflation, or excessive muscle work load/metabolic demand).

Nonetheless, having more intricate data available to monitor breathing pattern behavior during weaning may be helpful in the few patients who are very difficult to wean. As these difficult-to-wean patients consume an inordinate amount of clinical resources, the higher level of invasive monitoring may be justified. Regardless of whether or not NAVA becomes widely used, the clinical knowledge gained from more advanced respiratory muscle monitoring may be the most important feature of this mode.

Unplanned Extubation

Unplanned extubations include the accidental dislodgement of an endotracheal tube by clinicians or self-extubation by patients, the consequences of which can be catastrophic at worse, while often prolonging the duration of mechanical ventilation.[23] As such, a relatively high incidence of unplanned extubation is considered a marker of poor quality care, and therefore it behooves hospitals to monitor its incidence as part of overall quality improvement.[24] The incidence of unplanned extubation is reported to be approximately 7 per 100 ventilated patients, or 1 per 100 ventilation days.[7] Da Silva and Fonseca[7] published a comprehensive review of the topic to aid critical care clinicians who wish to establish a quality improvement project to minimize the incidence of unplanned extubation in their institutions.

The authors' review found several risk factors associated with a higher incidence for unplanned extubation. Some of these include increased level of consciousness and a higher incidence during the weaning phase. This may suggest that the process of weaning and extubation trials are not expeditious enough, as 30–70% of unplanned extubations do not require reintubation.[25] Other factors, such as agitation, inadequate sedation, and use of partial

versus full ventilatory support modes, also may suggest the same problem. Alternatively, it might suggest the opposite problem of inadequate ventilatory support and/or sedation/analgesia practices during the acute phase of critical illness. An important issue that is easy to correct is a change in practice by securing the endotracheal tube to the upper lip with waterproof twill or adhesive tape. A more nettlesome problem is staffing, as the incidence of unplanned extubation increases during the night shift, when healthcare personnel are not at the bedside, and also with nurses who have less than 5 years of clinical experience. Fortunately, the authors also cite evidence that instituting quality improvement measures is highly effective in minimizing the problem of unplanned extubation.

Noninvasive Ventilation for Acute Respiratory Failure

There continues to be much academic and clinical interest in noninvasive ventilation (NIV). A PubMed search was conducted of the following key words: non-invasive positive pressure ventilation, noninvasive positive pressure ventilation, noninvasive positive-pressure ventilation, non-invasive ventilation, noninvasive ventilation, nasal ventilation, bi-level positive airway pressure, bilevel positive airway pressure, bipap, date range January 1, 2012 to September 30, 2012, human, English language, age of 19+ years. This search returned 252 results, of which 17 are reviewed here.

A comparative effectiveness review was prepared for the Agency for Healthcare Research and Quality.[26] The review included 44 studies (4,122 subjects) that compared NIV to supportive care, 5 studies (405 subjects) that compared NIV to invasive ventilation, 12 studies (1,520 subjects) that compared bi-level positive airway pressure to CPAP, and 12 studies (1,463 subjects) that evaluated NIV for weaning from mechanical ventilation or in patients post-extubation. The greatest number of studies were conducted in patients with acute respiratory failure due to congestive heart failure or severe exacerbation of COPD. Compared with supportive care, NIV reduced hospital mortality (odds ratio [OR] 0.56, 95% confidence interval [CI] 0.44–0.72), intubation rate (OR 0.31, 95% CI 0.23–0.41), and hospital-acquired pneumonia. Compared with conventional weaning from invasive ventilation, NIV was associated with lower hospital mortality (OR 0.17, 95% CI 0.05–0.65) and a decreased rate of hospital-acquired pneumonia (OR 0.14, 95% CI 0.04–0.48) in patients with COPD. When used to prevent recurrent respiratory failure post-extubation, NIV decreased mortality (OR 0.60, 95% CI 0.34–1.04) and reintubation (OR 0.43, 95% CI 0.24–0.77), but only in those at high risk. Effects on mortality were smaller in studies with more characteristics of effectiveness trials, but did not differ for intubation rates. Effects did not differ by clinical setting or geographical region.

Patient Selection

Using data from the Healthcare Cost and Utilization Project's Nationwide In-patient Sample, Chandra et al[27] evaluated the prevalence and trends of NIV for COPD exacerbations. An estimated 7,511,267 admissions for COPD exacerbations occurred from 1998 to 2008. During this time, there was a 462% increase in NIV use, from 1.0% to 4.5% of all admissions, and a 42% decline in the use of invasive mechanical ventilation, from 6.0% to 3.5% of all admissions. This was accompanied by an increase in the percentage of patients who transitioned from NIV to invasive mechanical ventilation, and in-hospital mortality in this group worsened over time. In 2008, patients failing NIV and transitioning to invasive ventilation had a 29% mortality rate, which represented a 61% higher odds of death, compared with patients directly placed on invasive ventilation (95% CI 24–109%) and a 677% greater odds of death, compared with patients treated with NIV alone (95% CI 475–948%). With the exception of patients transitioned from NIV to invasive ventilation, hospital outcomes were favorable and improved steadily over the time period of this study. The authors concluded that NIV use increased significantly over time in patients hospitalized for COPD exacerbations, but the need for intubation and hospital mortality had declined. However, the rising mortality rate in a small but expanding group of patients requiring invasive mechanical ventilation after treatment with NIV is of concern; investigation into strategies to improve outcomes in this group is warranted.

Carrillo et al[28] prospectively assessed 716 consecutive patients: 173 with obesity hypoventilation syndrome, and 543 with COPD, all with acute hypercapnic respiratory failure. Patients with obesity hypoventilation syndrome were older, were more frequently female, had fewer late NIV failures, had lower hospital mortality, and had higher 1-year survival (OR 1.83, 95% CI 1.24–2.69, $P < .002$). However, survival adjusted for confounders, NIV failure, stay, and hospital re-admission were each similar between the groups. Among patients with COPD, obesity was associated with less late NIV failure and hospital readmission. The authors concluded that patients with obesity hypoventilation syndrome and acute hypercapnic respiratory failure treated with NIV have similar efficacy and better outcomes than patients with COPD.

High-intensity NIV has been proposed for use in patients with hypercapnic COPD. In a physiological randomized crossover study, Lukacsovits et al[29] assessed the short-term effects of 2 settings of NIV. One setting was aimed at maximally reducing P_{aCO_2} (high-intensity NIV) with an inspiratory positive airway pressure of 28 ± 2 cm H_2O, expiratory positive airway pressure of 4 cm H_2O, and breathing frequency of 22 breaths/min. The other setting used low-intensity NIV with an inspiratory positive airway

pressure of 18 ± 2 cm H_2O, expiratory positive airway pressure of 4 cm H_2O, and breathing frequency of 12 breaths/min. Both approaches significantly improved gas exchange, compared with spontaneous breathing, but to a greater extent using high-intensity NIV. High-intensity NIV also resulted in a greater reduction in the pressure-time product of the diaphragm. In 9 of 15 subjects, high-intensity NIV completely abolished spontaneous breathing. However, high-intensity NIV also induced a marked reduction in cardiac output, compared with low-intensity NIV. The authors concluded that, while high-intensity NIV was more effective than low-intensity NIV in improving gas exchange and in reducing inspiratory effort, it induces a marked reduction in cardiac output. Although this study is informative regarding the physiologic effects of high-intensity NIV, evidence of improved patient outcomes is needed before widespread application of this approach.

The role of NIV for patients with mild ARDS (P_{aO_2}/F_{IO_2} of 200–300 mm Hg) is controversial. Zhan et al[30] compared the safety and efficacy of NIV versus high-concentration oxygen therapy in this patient population. This was a multicenter randomized controlled trial of 40 subjects, conducted in 10 ICUs. The use of NIV was associated with a decreased breathing frequency and improved P_{aO_2}/F_{IO_2} over time. The proportion of patients requiring intubation, and the actual number of intubations, in the group receiving NIV was significantly less than in the control group (1 of 21 vs 7 of 19, $P = .02$, and 1 of 21 vs 4 of 19, $P = .04$, respectively). In-hospital mortality was lower in the group receiving NIV, but this was not significant (1 of 21 vs 5 of 19, $P = .09$). The number of organ failures in the NIV group was significantly lower than in the control group (3 vs 14, $P < .001$). The authors concluded that NIV is safe for selected patients with mild ARDS. Although NIV might be considered in patients with mild ARDS, patients must be carefully selected, and extreme caution is prudent when NIV is considered for patients with moderate or severe ARDS ($P_{aO_2}/F_{IO_2} < 200$ mm Hg).

Another controversial use of NIV is in patients with severe acute respiratory failure due to community-acquired pneumonia. In a prospective observational study of 184 consecutive subjects, Carrillo et al[31] applied NIV; 102 had de novo respiratory failure, and 82 had previously diagnosed cardiac or respiratory disease. NIV failed more frequently in subjects with de novo respiratory failure than in those with previous cardiac or respiratory disease (46% vs 26%, $P = .007$). A longer duration of NIV before intubation was associated with decreased hospital survival (adjusted OR 0.98, 95% CI 0.96–0.99, $P = .01$), but this association was not observed in patients with previous cardiac or respiratory disease. The authors concluded that successful NIV was strongly associated with better survival, but if predictors for NIV failure are present, avoiding delayed intubation of patients with de novo respiratory failure may minimize mortality.

Two papers evaluated the use of NIV in elderly patients. Schortgen and colleagues[32] conducted a prospective cohort study of all patients admitted to the medical ICU of a tertiary hospital during a 2-year period and managed using NIV. Very old patients (≥ 80 years) received NIV more frequently with do-not-intubate orders than in younger patients (40% vs 8%). Six-month mortality was 51% in very old patients, 67% in do-not-intubate patients, and 77% in patients with NIV failure and endotracheal intubation. The authors concluded that very old patients managed with NIV have an overall satisfactory 6-month survival. Kida et al[33] evaluated the use of NIV in 42 patients over the age of 75 years and with acute hypercapnic respiratory failure. All patients with a Glasgow Coma scale score ≥ 9 and/or an APACHE II score < 29 survived after the initiation of NIV.

Garcia-Delgado et al[34] conducted a retrospective study in 63 subjects to evaluate the use of NIV associated with respiratory failure after extubation in subjects after cardiac surgery. The median time from extubation to the NIV application was 40 hours (18–96 hours). NIV failed in 52% of subjects who had a lower pH at 24 hours of treatment and a higher hospital mortality (52% vs 7%, $P = .001$) than those in whom NIV was successful. An interval < 24 hours from extubation to NIV was a predictive factor for NIV failure (OR 4.6, 95% CI 1.2–17.9), whereas obesity was associated with NIV success (OR 0.22, 95% CI 0.05–0.91). The authors concluded that reintubation was required in half of the NIV-treated patients and was associated with an increased hospital mortality rate.

Su et al[35] conducted a prospective, multicenter randomized controlled study of subjects receiving mechanical ventilation for > 48 hours who tolerated a 2-hour SBT and were subsequently extubated. The 406 subjects were randomized to NIV or standard medical therapy. There were no differences in extubation failure (13.2% in control and 14.9% in NIV), ICU mortality, or hospital mortality. Abundant secretions were the most common reason for extubation failure. In this study, preventive use of NIV after extubation in subjects who passed an SBT did not show benefits in decreasing extubation failure rate or the mortality rate. Rather than apply NIV routinely to all patients after extubation, its use should be reserved to those subjects considered to be at high risk for recurrent respiratory failure.[26,36] Its use in patients at low risk for post-extubation respiratory failure, such as those in the study by Su et al, is not recommended.[37]

Robust evidence supports the use of respiratory therapist directed protocols for weaning and discontinuation of invasive mechanical ventilation.[38] Duan and colleagues[39] conducted a prospective, randomized controlled trial of a respiratory therapist protocol for weaning from NIV. There

were 73 subjects successfully weaned from NIV in the protocol-directed group, and 36 subjects in the physician-directed group. Compared with physician-directed weaning, protocol-directed weaning reduced the duration of NIV (4.4 ± 2.5 d vs 2.6 ± 1.5 d, respectively, $P < .001$) and the duration of the ICU stay (8.1 ± 5.5 d vs 5.8 ± 2.7 d, respectively, $P = .02$). The authors concluded that protocol-directed weaning reduces the duration of NIV and the duration of the ICU stay.

Setting

Roessler et al[40] enrolled 51 subjects into a randomized controlled trial to assess whether out-of-hospital application of NIV is feasible, safe, and more effective, compared with standard medical therapy. NIV was found to be safe and effective in all subjects. In the standard medical therapy group, treatment was not effective in 5 of 25 subjects ($P = .05$). Subjects in the standard medical therapy group were admitted to an ICU more frequently and for longer periods, compared with subjects in the NIV group. In the standard medical therapy group, 6 subjects required subsequent in-hospital intubation, compared with only 1 subject in the NIV group. Subjects in the NIV group received NIV more frequently in hospital, compared with subjects in the standard medical therapy group ($P < .01$). The authors concluded that NIV should be the first-line treatment in out of hospital acute respiratory failure, if no contraindications are present.

Although NIV is used outside the ICU for patients with acute respiratory failure, success and failure risk factors and patient safety aspects have been poorly explored in this setting. Cabrini et al[41] prospectively interviewed 45 consecutive subjects successfully treated with NIV for acute respiratory failure outside the ICU. More than 40% reported that they never had the possibility to discuss the NIV treatment, and 80% reported they were never asked to try another interface. All subjects knew how to call for help, but only 25% had been trained to remove the mask, and 22% reported not being able to remove the mask if needed. Half of the subjects reported having received help immediately when needed, but 15% waited more than 3 min. All subjects reported complications, and 18% reported respiratory worsening while on NIV. The authors concluded that subjects reported a low level of involvement in the initial setting of NIV treatment, low satisfaction about communication with the caring staff, and a suboptimal safety level in case of emergency. This should inform the practice of all of us who care for patients receiving NIV, suggesting that we should involve our patients more in the initiation of this therapy.

Technical Aspects

A well known complication of NIV is nasal ulcerations. A total face mask, which has no contact with the more sensitive areas of the face, is an option to address this problem. Belchior and colleagues[42] described 3 patients with acute respiratory failure due to amyotrophic lateral sclerosis, who developed nasal bridge skin necrosis during continuous NIV, and 1 patient with post-extubation respiratory failure due to a high spinal cord injury, who had facial trauma with contraindication for conventional mask use. In each of these patients, the total face mask was well tolerated and permitted safe and efficient continuous NIV for several days until the acute respiratory failure resolved. None of the patients required endotracheal intubation during the acute episode. This interface may be an effective option for patients who develop complications or who are intolerant of other interfaces for NIV.

Although different kinds of ventilators are available to perform NIV in the ICU, the ventilator that allows the best patient-ventilator synchrony is unknown. The objective of the study by Carteaux et al[43] was to compare patient-ventilator synchrony with ICU ventilators with or without their NIV algorithm engaged, transport ventilators with or without their NIV algorithm engaged, and dedicated NIV ventilators. A bench model simulating spontaneous breathing efforts was used to assess the impact of inspiratory and expiratory leaks on cycling and triggering functions in 19 ventilators. This was followed by a clinical study to evaluate the incidence of asynchrony in 15 subjects during 3 randomized consecutive 20 min-periods of NIV using an ICU ventilator with and without its NIV algorithm engaged, and a dedicated NIV ventilator. In the bench study, frequent auto-triggering and delayed cycling occurred in the presence of leaks using ICU and transport ventilators. NIV algorithms unevenly minimized these asynchronies, whereas no asynchrony was observed with the dedicated NIV ventilators in all but one. In the clinical study the asynchrony index was significantly lower with a dedicated NIV ventilator than with the ICU ventilators with or without their NIV algorithm engaged. The authors concluded that dedicated NIV ventilators allow better patient-ventilator synchrony than ICU and transport ventilators. The NIV algorithm improves, at least slightly and with a wide variation among ventilators, trigger and/or cycle synchrony. Because of the variability of performance among ventilators that can be used for NIV, it is important that the clinician be familiar with the function of the specific ventilator used when leaks are present, such as with NIV.[44]

Schmidt et al[45] compared the impact of PSV and NAVA, with and without an NIV algorithm, on patient-ventilator interaction in 17 subjects receiving post-extubation NIV. Subjects were randomly ventilated for 10 min with PSV without an NIV algorithm, PSV with an NIV algorithm, NAVA without an NIV algorithm, and NAVA with an NIV algorithm. For both PSV and NAVA, the NIV algorithm significantly reduced the effect of leakage ($P < .01$).

Inspiratory trigger delay was not affected by the NIV algorithm, but was shorter with NAVA than with PSV ($P < .01$). Excess inspiratory time (poor cycle) was shorter in NAVA and PSV with the NIV algorithm than in PSV without the NIV algorithm ($P < .05$). The asynchrony index was not affected by the NIV algorithm, but was significantly lower with NAVA than with PSV ($P < .05$). The asynchrony index caused by leaks was insignificant with NAVA and lower than with PSV ($P < .05$). There was more double triggering with NAVA. The authors concluded that NAVA with the NIV algorithm offers the best compromise between good patient-ventilator synchrony and a low level of leak. One issue with NAVA is the need for a special nasogastric catheter. As recognized by the authors, the presence of the nasogastric catheter may magnify leaks. Before recommending the use of NAVA for NIV, high-level studies reporting improved patient outcomes with this technique will be needed.

Cystic Fibrosis

CF is a life-limiting autosomal recessive disorder affecting approximately 80,000 individuals worldwide. Scientific progress in the understanding of the pathophysiology of CF, and advancements in clinical treatment have improved the median predicted survival rate and quality of life for those affected by this disease.[46] Clinical investigations contributed to new medications and treatments for the pulmonary and non-pulmonary manifestations of this disease. The 4 key pillars of CF care include prompt identification and treatment of pulmonary infections, suppression of airways inflammation, relief of airway obstruction, and attention to nutritional status and nutritional support.[47] A PubMed search was conducted of peer-reviewed manuscripts published from January 1 to December 31, 2012, using the following key-terms: cystic fibrosis, treatment guidelines, adherence, survival, prognosis, and lung function. This search identified 40 papers, of which 10 were selected for review: 6 original research papers and 4 review articles.

The CF Therapeutic Development Network

The Cystic Fibrosis Foundation has been instrumental in supporting scientific investigations for the development and evaluation of new therapies for CF treatment.[48] Rowe and colleagues[49] presented a brief history of the development, structure, and function of the CF Therapeutic Development Network, and discussed the progress it has made since its inception in 1998. The authors also present scientific advancements within each of the pillars of CF care, as well as approved and emerging approaches to altering the basic gene defect. Since identification of the basic gene defect,[50] there has been no evidence to support the use of CF transmembrane regulator (CFTR) gene transfer as a treatment for lung disease. However, the authors of this review highlight the progress that has been made in modulating mutant CFTR protein to facilitate a function that is closer to normalcy. The authors emphasized studies that affected the quantity of the CFTR protein that reached the cell surface and function of the CFTR channel at the cell surface. Specifically, they present results of clinical trials that led to the first approved CFTR potentiator, ivacaftor (Kalydeco, Vertex Pharmaceuticals, Boston, Massachusetts). Ivacaftor is indicated for a specific mutation, G551D, and augments the chloride-transport activity of G551D-CFTR protein by increasing the time that activated CFTR channels at the cell surface remain open. The authors report results from original clinical investigations demonstrating statistically significant improvements in FEV_1, weight gain, respiratory symptoms, and quality of life, as well as a significant reduction in sweat chloride concentration among subjects treated with ivacaftor, compared to placebo. This review also discusses the status of the CF Therapeutic Development Network sponsored clinical investigations dedicated to CFTR-based therapies for other CFTR mutations.

Treatment of Infections

Prompt identification and treatment of pulmonary infections is an essential component of CF care. Pulmonary exacerbations are associated with inflammation and impaired mucociliary clearance, which contributes to worsening airways obstruction, a decline in lung function, and a profound negative impact on perceived quality of life. Three longitudinal studies addressed the identification of and risk factors for pulmonary exacerbations.

Pulmonary exacerbations are typically identified by clinical signs and symptoms and treatment plans, based upon the clinician's perception of the presence and severity of those symptoms. Identifying pulmonary exacerbations in young children can be particularly challenging. The investigators of the Epidemiologic Study of Cystic Fibrosis[51] approached this problem using a large data set of clinical characteristics and the clinician's treatment decision to treat to confirm the signs and symptoms that identify and prompt treatment for an exacerbation in young children. They found that increased cough, new onset crackles, increased sputum production, and relative decline in weight for age percentile of $> 45\%$ was associated with treatment for pulmonary exacerbation in children < 6 years of age. In addition to confirming the clinical signs and symptoms associated with identification and likelihood for physicians to treat a pulmonary exacerbation, these authors noted that patients treated with inhaled, intravenous, and/or oral quinolone antibiotic therapy for an exacerbation were more likely to be free of cough and adventitious breath sounds such as crackles and wheezes, as well as *Pseudomonas*

aeruginosa detected in a sputum culture at a follow-up clinic visit within 6 months of treatment.

Sequeiros and Jarad[52] conducted a 3-year longitudinal study evaluating the risk factors associated with a shortened time between exacerbations in adult patients with CF. They enrolled 58 subjects with chronic infection caused by organisms other than *Burkholderia cepacia*. Subjects were prospectively followed and treated with intravenous antibiotics for 170 pulmonary exacerbations during the study period. The authors reported a higher incidence of CF-related complications such as CF-related diabetes, presence of *P. aeruginosa* infections, and allergic bronchopulmonary aspergillosis than rates previously reported in the literature. Older patients with poorer lung function at the end of the treatment course (as determined by percentage predicted FEV_1) were at a significantly higher risk for a shorter time between exacerbations. These findings suggest close follow-up of at-risk patients at the end of a treatment course for pulmonary exacerbation may improve prompt recognition of clinical characteristics associated with exacerbation, improve the propensity for out-patient treatment, and minimize the time until the next pulmonary exacerbation requiring intravenous antibiotics. In addition to clinical characteristics, the change in percentage predicted FEV_1 is often used to quantify lung function decline, and influences the patient's treatment plan.

Danish investigators[53] followed 479 patients over a 41-year period to explore factors influencing the variability in percentage FEV_1 measurements in a data set of 70,448 lung function measurements. Pancreatic insufficiency and acquisition of *P. aeruginosa* were the covariates that had the most profound effect on rate of decline in lung function, while the comorbidity of CF-related diabetes had no effect on the rate of decline in lung function for the study population. In this investigation the authors present a mathematical model that can be utilized to minimize variance in $\%FEV_1$ to assist clinicians in quantifying changes in $\%FEV_1$ over time. By identifying clinical characteristics associated with the risk for airway obstruction, malnutrition, and decline in lung function, clinicians may be better equipped to promptly recognize and treat pulmonary exacerbations, which can ultimately improve their patient's long-term prognosis.

Adherence to Guidelines

The pillars of CF care credited with improving longevity and the quality of life involve the implementation of multiple strategies to prevent and treat the multisystem manifestations of this disease and its associated comorbidities. Based upon published evidence, the Cystic Fibrosis Foundation established guidelines for the maintenance of lung health and prevention of pulmonary exacerbations. Commissioned and modified systematic reviews and Cochrane reviews were used to construct the aforementioned guidelines published in 2007.[54]

Adherence to the CF Foundation pulmonary guidelines was of particular interest to Glauser et al.[55] They conducted a survey of pulmonologists practicing in accredited CF centers to determine physicians' familiarity and agreement with the perceived usefulness of the guidelines in reducing exacerbations and improving or maintaining lung function, as well as to identify guideline, patient, and processor system-related barriers to implementing the guidelines. Most (90%) of the 98 respondents considered themselves familiar with the CF guidelines and agreed that the guidelines were useful (90%) and relevant (91%), and followed them (85%) when caring for patients with CF. Nearly half the physicians responding to the survey reported that patient barriers affected their ordering practices, citing the high cost of medications (44%), burdensome treatment regimens (46%), and non-adherence to prescribed medications (53%) as factors that prevented or substantially prevented them from adhering to the CF guidelines.

In a review of the challenges and opportunities in managing CF pulmonary disease and related comorbidities, Sawicki and Tiddens[56] concurred with the findings of Glauser and colleagues,[55] but also reported that optimal management may be hindered by other patient-related factors, such as depression, lack of disease-related education aimed at performing airway clearance therapies properly, and understanding medication/therapy regimens to promote self-care. Adverse effects of therapy, such as toxicity, unpalatable taste and drug interactions, inconvenience of medication delivery systems and airway clearance modalities, as well as lack of clinician time dedicated to patient/family education, were cited as deterrents to adhering to the prescribed plans of care.

Inhaled hypertonic saline is one of the medications recommended for the maintenance of lung health and prevention of pulmonary exacerbations for patients 6 years of age or older. Age restricted recommendations were based on lack of evidence evaluating the safety and efficacy of this therapy in young children. The Infant Study of Inhaled Saline in Cystic Fibrosis (ISIS)[57] addressed this knowledge gap though a prospective randomized multicenter double-blinded placebo controlled study. A total of 321 patients between the ages of 4 and 60 months participated in a 48 week trial, which demonstrated that, although inhaled hypertonic saline was well tolerated and adhered to, this therapy did not reduce the rate of pulmonary exacerbations when compared with isotonic saline.

Although the prompt treatment of airways obstruction, infection, and inflammation are key components of care for CF patients, complicated treatment regimens and lengthy treatment times contribute to non-adherence. Technological advances in antimicrobial therapy and inhaled delivery systems bring the promise of improved tolerance,

reduced treatment times, and enhanced adherence to recommended care. In a comprehensive review of antimicrobial therapy and inhaled delivery systems, the clinician is provided with a summary of the published evidence on approved agents and characteristics of clinical trials for those in the therapeutic development pipeline.[58]

Attention to nutritional status and focus on nutritional support is one of the pillars of CF care and the topic of the final paper selected for the 2012 year in review for CF care. Often respiratory therapists are preoccupied with pulmonary manifestations of CF care, directed toward ensuring inhaled medications and airway clearance therapies are performed properly, in a timely manner, and continually evaluated for therapeutic effectiveness.[59-61] The literature demonstrates an interrelationship between lung function and nutritional status.[62,63] Current recommendations for caloric intake, nutritional supplements, and pancreatic enzyme replacement therapy are provided in a comprehensive review of new and emerging therapies for the maintenance of nutritional status in patients with CF.[64] This in depth discussion of the challenges to and need for nutritional support provides clinicians with an evidence-based formula for successful surveillance and care plan strategies to favorably impact both nutritional status and lung function.

Summary

In this paper the important recent literature on invasive mechanical ventilation, noninvasive ventilation, and CF is reviewed. It is our hope that this will help to familiarize the reader with the important literature in these subject areas.

REFERENCES

1. Macintyre NR, Nava S, DiBlasi RM, Restrepo RD, Hess DR. Respiratory care year in review 2010: part 2. Invasive mechanical ventilation, noninvasive ventilation, pediatric mechanical ventilation, aerosol therapy. Respir Care 2011;56(5):667-680.
2. Rubin BK, Dhand R, Ruppel GL, Branson RD, Hess DR. Respiratory care year in review 2010: part 1. Asthma, COPD, pulmonary function testing, ventilator-associated pneumonia. Respir Care 2011; 56(4):488-502.
3. Dunne PJ, Macintyre NR, Schmidt UH, Haas CF, Jones-Boggs Rye K, Kauffman GW, Hess DR. Respiratory care year in review 2011: long-term oxygen therapy, pulmonary rehabilitation, airway management, acute lung injury, education, and management. Respir Care 2012;57(4):590-606.
4. Needham DM, Colantuoni E, Menez-Tellez PA, Dinglas VD, Sevransky JE, Dennison Himmelfarb CR, et al. Lung protective mechanical ventilation and two year survival in patients with acute lung injury: prospective cohort study. BMJ 2012;344:e2124.
5. Guo F, Chen J, Liu S, Yang C, Yang Y. Dead space fraction changes during PEEP titration following lung recruitment in patients with ARDS. Respir Care 2012;57(10):1578-1585.
6. Liu L, Liu H, Yang Y, Huang Y, Liu S, Beck S, et al. Neuroventilatory efficiency and extubation readiness in critically ill patients. Crit Care 2012;16(4):R143.
7. da Silva PS, Fonseca MC. Unplanned endotracheal extubations in the intensive care unit: systematic review, critical appraisal, and evidence-based recommendations. Anesth Analg 2012;114(5):1003-1014.
8. NHLBI Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as a compared with traditional tidal volumes for acute respiratory distress syndrome. N Engl J Med 2000; 342(18):1301-1308.
9. Rubenfeld GD, Herridge MS. Epidemiology and outcomes of acute lung injury. Chest 2007;131(2):554-562.
10. Chiumello D, Taccone P, Berto V, Marino A, Migliara G, Lazzerini M, Gattinoni L. Long-term outcomes in survivors of acute respiratory distress syndrome ventilated in supine or prone position. Intensive Care Med 2012;38(2):221-229.
11. Rubenfeld GD, Caldwell E, Hudson L. Publication of study results does not increase use of lung-protective strategy in patients with acute lung injury (abstract). Am J Respir Crit Care Med 2001;163A: 295.
12. Gajic O, Dara SI, Mendez JL, Adesanya O, Festic E, Caples SM, et al. Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. Crit Care Med 2004; 32(9):1817-1824.
13. Determann RM, Royakkers A, Wolthius EK, Vlaar AP, Choi G, Paulus F, et al. Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: a preventative randomized controlled trial. Crit Care 2010;14(1):R1.
14. Lellouche F, Dionne S, Simard S, Bussieres J, Dagenais F. High tidal volumes in mechanically ventilated patients increase organ dysfunction after cardiac surgery. Anesthesiology 2012;116(5):1072-1082.
15. Suter PM, Fairley HB, Isenberg MD. Optimum end-expiratory airway pressure in patients with acute pulmonary failure. N Engl J Med 1975;292(6):284-289.
16. Gattinoni L, Presenti A, Torresin A, Baglioni S, Rivolta M, Rossi F, et al. Adult respiratory distress syndrome profiles by computed tomography. J Thorac Imag 1986;1(3):25-30.
17. Maunder RJ, Shuman WP, McHugh JW, Marglin SI, Butler J. Preservation of normal lung regions in the adult respiratory distress syndrome. Analysis by computed tomography. JAMA 1986;255(18): 2463-2465.
18. Tusman G, Suarez-Sipmann F, Böhm SH, Pech T, Reismann H, Meschino G, et al. Monitoring dead-space during recruitment and PEEP titration in an experimental model. Intensive Care Med 2006; 32(11):1863-1871.
19. Maisch S, Reismann H, Fuellekrug B, Weismann D, Rutkowski T, Tusman G, Bohm SH. Compliance and dead-space fraction indicate an optimal level of positive end-expiratory pressure after recruitment in anesthetized patients. Anesth Analg 2008;106(1):175-181.
20. Girgis K, Hamed H, Khater Y, Kacmarek RM. A decremental PEEP trial identifies the PEEP level that maintains oxygenation after lung recruitment. Respir Care 2006;51(10):1132-1139.
21. Kallet RH. Measuring dead-space in acute lung injury. Minerva Anestesiol 2012;78(11):1297-1305.
22. Kacmarek RM. Proportional assist ventilation and neurally adjusted ventilatory assist. Respir Care 2011;56(2):140-152.
23. Epstein SK, Nevins ML, Chung J. Effect of unplanned extubation on outcome of mechanical ventilation. Am J Respir Crit Care Med 2000;161(6):1912-1916.
24. Peñuelas Ó, Frutos-Vivar F, Esteban A. Unplanned extubation in the ICU: a marker of quality assurance of mechanical ventilation. Crit Care 2011;15(2):128.
25. Listello D, Sessler CN. Unplanned extubation: clinical predictors for reintubation. Chest 1994;105(5):1496-1503.
26. Williams JW Jr, Cox CE, Hargett CW, Gilstrap DL, Castillo CE, Govert JA, et al. Noninvasive positive-pressure ventilation (NPPV) for acute respiratory failure. Rockville (MD): Agency for Healthcare

Research and Quality; 2012: Comparative effectiveness review no. 68. http://www.ncbi.nlm.nih.gov/books/NBK99179/pdf/TOC.pdf. *Accessed February 1, 2013.*
27. Chandra D, Stamm JA, Taylor B, Ramos RM, Satterwhite L, Krishnan JA, et al. Outcomes of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease in the United States, 1998-2008. Am J Respir Crit Care Med 2012;185(2):152-159.
28. Carrillo A, Ferrer M, Gonzalez-Diaz G, Lopez-Martinez A, Llamas N, Alcazar M, et al. Noninvasive ventilation in acute hypercapnic respiratory failure caused by obesity hypoventilation syndrome and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2012;186(12):1279-1285.
29. Lukacsovits J, Carlucci A, Hill N, Ceriana P, Pisani L, Schreiber A, et al. Physiological changes during low- and high-intensity noninvasive ventilation. Eur Respir J 2012;39(4):869-875.
30. Zhan Q, Sun B, Liang L, Yan X, Zhang L, Yang J, et al. Early use of noninvasive positive pressure ventilation for acute lung injury: a multicenter randomized controlled trial. Crit Care Med 2012;40(2): 455-460.
31. Carrillo A, Gonzalez-Diaz G, Ferrer M, Martinez-Quintana ME, Lopez-Martinez A, Llamas N, et al. Non-invasive ventilation in community-acquired pneumonia and severe acute respiratory failure. Intensive Care Med 2012;38(3):458-466.
32. Schortgen F, Follin A, Piccari L, Roche-Campo F, Carteaux G, Taillandier-Heriche E, et al. Results of noninvasive ventilation in very old patients. Ann Intensive Care 2012;2(1):5.
33. Kida Y, Minakata Y, Yamada Y, Ichinose M. Efficacy of noninvasive positive pressure ventilation in elderly patients with acute hypercapnic respiratory failure. Respiration 2012;83(5):377-382.
34. Garcia-Delgado M, Navarrete I, Garcia-Palma MJ, Colmenero M. Postoperative respiratory failure after cardiac surgery: use of noninvasive ventilation. J Cardiothorac Vasc Anesth 2012;26(3):443-447.
35. Su CL, Chiang LL, Yang SH, Lin HI, Cheng KC, Huang YC, et al. Preventive use of noninvasive ventilation after extubation: a prospective, multicenter randomized controlled trial. Respir Care 2012; 57(2):204-210.
36. Hess DR. The role of noninvasive ventilation in the ventilator discontinuation process. Respir Care 2012;57(10):1619-1625.
37. Figueroa-Casas JB. Preventive use of noninvasive ventilation after planned extubation. Respir Care 2012;57(2):318-320.
38. Haas CF, Loik PS. Ventilator discontinuation protocols. Respir Care 2012;57(10):1649-1662.
39. Duan J, Tang X, Huang S, Jia J, Guo S. Protocol-directed versus physician-directed weaning from noninvasive ventilation: the impact in chronic obstructive pulmonary disease patients. J Trauma Acute Care Surg 2012;72(5):1271-1275.
40. Roessler MS, Schmid DS, Michels P, Schmid O, Jung K, Stober J, et al. Early out-of-hospital non-invasive ventilation is superior to standard medical treatment in patients with acute respiratory failure: a pilot study. Emerg Med J 2012;29(5):409-414.
41. Cabrini L, Moizo E, Nicelli E, Licini G, Turi S, Landoni G, et al. Noninvasive ventilation outside the intensive care unit from the patient point of view: a pilot study. Respir Care 2012;57(5):704-709.
42. Belchior I, Goncalves MR, Winck JC. Continuous noninvasive ventilation delivered by a novel total face mask: a case series report. Respir Care 2012;57(3):449-453.
43. Carteaux G, Lyazidi A, Cordoba-Izquierdo A, Vignaux L, Jolliet P, Thille AW, et al. Patient-ventilator asynchrony during noninvasive ventilation: a bench and clinical study. Chest 2012;142(2):367-376.
44. Hess DR, Branson RD. Know your ventilator to beat the leak. Chest 2012;142(2):274-275.
45. Schmidt M, Dres M, Raux M, Deslandes-Boutmy E, Kindler F, Mayaux J, et al. Neurally adjusted ventilatory assist improves patient-ventilator interaction during postextubation prophylactic noninvasive ventilation. Crit Care Med 2012;40(6):1738-1744.
46. Cystic Fibrosis Foundation. CFF annual report 2011: adding tomorrows. http://www.cff.org/uploadedFiles/aboutCFFoundation/AnnualReport/2011-Annual-Report.pdf. *Accessed February 1, 2013.*
47. Cohen-Cymberknoh M, Shoseyov D, Kerem E. Managing cystic fibrosis: strategies that increase life expectancy and improve quality of life. Am J Respir Crit Care Med 2011;183(11):1463-1471.
48. Marshall BC, Penland CM, Hazle L, Ashlock M, Wetmore D, Campbell PW 3rd, Beall RJ. Cystic fibrosis foundation: achieving the mission. Respir Care 2009;54(6):788-795.
49. Rowe SM, Borowita DS, Burns JL, Clancy JP, Donaldson SH, Retsch-Bogart G, et al. Progress in cystic fibrosis and the CF therapeutics development network. Thorax 2012;67(10):882-890.
50. Kerem B, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, et al. Identification of the cystic fibrosis gene: genetic analysis. Science 1989;245(4922):1073-1080.
51. Regalmann WE, Schechter MS, Wagener JS, Morgan WJ, Pasta DJ, Elkin EP, Konstan MW; for the Investigators of the Epidemiologic Study of Cystic Fibrosis. Pulmonary exacerbations in cystic fibrosis: young children with characteristic signs and symptoms. Pediatr Pulmonol 2012 [ePub ahead of print]
52. Sequeiros IM, Jarad N. Factors associated with a shorter time until the next pulmonary exacerbation in adult patients with cystic fibrosis. Chron Respir Dis 2012;9(1):9-16.
53. Taylor-Robinson D, Whitehead M, Diderichsen F, Olesen HV, Pressler T, Smyth RL, Diggle P. Understanding the natural progression in % FEV_1 decline in patients with cystic fibrosis: a longitudinal study. Thorax 2012;67(10):860-866.
54. Flume PA, O'Sullivan BP, Robinson KA, Goss CH, Mogayzel PJ, Willey-Courand DB, et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. Am J Respir Crit Care Med 2007;176(10):957-969.
55. Glauser TA, Nevins PH, Williamson JC, Abdolrasulnia M, Salinas GD, Zhang J, et al. Adherence to the 2007 cystic fibrosis pulmonary guidelines: a national survey of CF care centers. Pediatr Pulmonol 2012;47(5):434-440.
56. Sawicki GS, Tiddens H. Managing treatment complexity in cystic fibrosis: challenges and opportunities. Pediatr Pulmonol 2012;47(6): 523-533.
57. Rosenfeld M, Ratjen F, Brumback L, Daniel S, Rowbotham R, McNamara S, et al; ISIS Study Group. Inhaled hypertonic saline in infants and children younger than 6 years with cystic fibrosis: the ISIS randomized controlled trial. JAMA 2012;307(21):2269-2277.
58. Hewer SL. Inhaled antibiotics in cystic fibrosis: what's new? J R Soc Med 2012;105(S2):S19-S24.
59. Richards KM, Lester MK, Chin MJ, Marshall BC. A preliminary evaluation of the effectiveness of the Cystic Fibrosis Foundation mentoring program for respiratory care. Respir Care 2012 [ePub ahead of print]
60. Flume PA, Robinson KA, O'Sullivan BP, Finder JD, Vender RL, Willey-Courand DB, et al. Cystic fibrosis pulmonary guidelines: airway clearance therapies. Respir Care 2009;54(4):522-537.
61. Lester MK, Flume PA. Airway-clearance therapy guidelines and implementation. Respir Care 2009;54(6):733-753.
62. Kraemer R, Aebi C, Casaulta Aebischer C, Gallati S. Early detection of lung disease and its association with the nutritional status, genetic background and life events in patients with cystic fibrosis. Respiration 2000;67(5):477-490.
63. Borowitz D. The interrelationship of nutrition and pulmonary function in patients with cystic fibrosis. Curr Opin Pulm Med 1996;2(6):457-461.
64. Kalnins D, Wilschanski M. Maintenance of nutritional status in patients with cystic fibrosis: new and emerging therapies. Drug Des Devel Ther 2012;6:151-161.