What Is Evidence-Based Medicine and Why Should I Care?

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The principles of evidence-based medicine provide the tools to incorporate the best evidence into everyday practice. Evidence-based medicine is the integration of individual clinical expertise with the best available research evidence from systematic research and the patient's values and expectations. A hierarchy of evidence can be used to assess the strength of evidence upon which clinical decisions are made, with randomized studies at the top of the hierarchy. The efficient approach to finding the best evidence is to identify a systematic review or evidence-based clinical practice guidelines. Calculated metrics, such as sensitivity, specificity, receiver-operating-characteristic curves, and likelihood ratios, can be used to examine the evidence for a diagnostic test. High-level studies of a therapy are prospective, randomized, blinded, placebo-controlled, have a concealed allocation, have a parallel design, and assess patient-important outcomes. Metrics used to assess the evidence for a therapy include event rate, relative risk, relative risk reduction, absolute risk reduction, number needed to treat, and odds ratio. Although not all tenets of evidence-based medicine are universally accepted, the principles of evidence-based medicine nonetheless provide a valuable approach to respiratory care practice. *Key words: likelihood ratio, meta-analysis, number needed to treat, receiver operating characteristic curve, relative risk, sensitivity, specificity, systematic review, evidence-based medicine.* [Respir Care 2004;49(7):730–741.

'In my clinical experience' is a phrase that usually introduces a statement of rank, prejudice, or bias. The information that follows it cannot be checked nor has it been subjected to any analysis other than some vague tally of the speaker's memory. The biases of eminent men are still biases.

—Michael Crichton*

Introduction

Without question, one of the more important movements impacting health care practice in the late 20th century was the emergence of "evidence-based medicine." Although many of the concepts inherent in the practice of

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*N Engl J Med 1971;285:1491.

Dean R. Hess PhD RRT FAARC presented a version of this report at the 19th Annual New Horizons Symposium at the 49th International Respiratory Congress, held December 8–11, 2003, in Las Vegas, Nevada.

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evidence-based medicine have been used for decades, the emergence of evidence-based medicine as a systematic, distinct entity is traced to an article published in the *Journal of the American Medical Association* in 1992.[1] From 1993 to 2000, 25 "Users Guides to the Medical Literature" were published and became the major force directing the evolution of evidence-based medicine.[2–31] In the early 21st century evidence-based medicine has permeated all parts of health care practice, including respiratory care.

Is There a Problem?

Respiratory care practice demands evidence for the accuracy of diagnostic tests. We also need evidence of efficacy and safety of the treatments that we apply. The traditional sources of this evidence are inadequate. Textbooks are outdated, information from experts is inadequate, lectures are ineffective, and professional journals are overwhelming. A paradox exists between our clinical assessment skills, which increase over time, and our knowledge, which decreases over time. We are often too busy with our professional and personal lives to read the exponentially increasing volumes of published research. The principles of evidence-based medicine provide the tools to incorporate the best evidence into everyday practice.

A recent study of arthroscopic knee surgery illustrates the need for evidence-based medicine. In the United States, 650,000 cases/y of osteoarthritis of the knee are treated with arthroscopic lavage or debridement, at a cost of about $5,000 each. Moseley et al[32] randomized 180 patients to lavage, debridement, or placebo surgery. Perhaps to the surprise of many, outcomes after surgery were no different than outcomes after the placebo procedure. This demonstrates the need for high-quality studies to establish the evidence for medical practice. Many physicians and patients are convinced of the benefit of that surgery, but without high-level evidence in support of that belief. In fact, prior to the Moseley et al study some might have argued that arthroscopic lavage or debridement for treatment of osteoarthritis of the knee was the standard of care and thus it would be unethical to subject patients to a placebo-controlled study. However, one might ask whether it is more unethical to do a study that deprives the patient of the conventional therapy or to subject the patient to an unproven therapy?

Lung-volume-reduction surgery is an example relevant to respiratory care practice. This surgery was proposed as a palliative treatment for severe emphysema, and several small trials suggested benefit.[33–40] A prospective, controlled trial of 1,218 patients with severe emphysema randomized patients to either undergo lung-volume-reduction surgery or to receive continued medical treatment.[41] Lung-volume-reduction surgery increased the likelihood of improved exercise capacity but did not confer a survival advantage over medical therapy—except in the subgroup who had both predominantly upper-lobe emphysema and low baseline exercise capacity. Moreover, the subgroup that had non-upper-lobe emphysema and high baseline exercise capacity had higher mortality and negligible functional gain. This is an example of a therapy for which there was much enthusiasm but little evidence in the late 20th century. A properly conducted study showed that there was no benefit expect for a subgroup of patients, and, equally important, there was harm to another subgroup.

What Is Evidence-Based Medicine?

Evidence-based medicine is the integration of individual clinical expertise with the best available evidence from systematic research, as well as patient's values and expectations.[42,43] The best evidence is not static but, rather, changes when better evidence becomes available.

Evidence-based medicine does not devalue clinical skills and clinical judgment. To the contrary, evidence-based medicine demands a high level of clinical skill and judgment. The practice of evidence-based medicine requires us to apply the evidence to the right patient, at the right time, in the right place, at the right dose, and using the right resources. We need to recognize the correct patient diagnosis before applying the evidence to the care of the patient. Use of the ARDS (acute respiratory distress syndrome) Network ventilation strategy[44] may be inappropriate with patients who have chronic obstructive pulmonary disease (COPD) or neuromuscular disease. As a matter of fact, those patient groups were excluded from enrollment in the ARDS Network study. Evidence-based guidelines for COPD are also available,[45] but these may not be relevant to patients with asthma or cystic fibrosis.

Research evidence comes from clinical research with intact patients. Animal studies do not trump patient studies. That is not to say that animal studies are not important to test proof-of-concept or to explore physiologic mechanisms. However, care must always be taken when extrapolating animal studies to patient care. The findings of properly conducted studies in a relevant patient population should never be discarded in favor of the findings from an animal study. No number of animal studies can outweigh the findings of even a single well-done human study. Animal studies and bench models can support human studies, but they cannot invalidate the results of well-done clinical studies.

Research evidence has a short doubling time—perhaps 10 years or less. Thus it can be a challenge for clinicians to stay abreast of the newest research findings. The evolving research evidence replaces currently accepted diagnostic tests and treatments with new ones that are more powerful, more accurate, more efficacious, and safer.

Patient values and expectations are an important part of evidence-based medicine. For example, there is a compelling body of high-level research evidence supporting the use of noninvasive positive-pressure ventilation (NPPV) for COPD exacerbation, in which NPPV decreases the risk of intubation and affords a survival benefit.[46,47] However, the patient suffering COPD exacerbation may choose not to accept NPPV. Some patients may elect intubation or tracheostomy instead of NPPV, and others may elect not to receive positive-pressure ventilation at all. Another example relates to the choice of aerosol delivery device. There is compelling evidence that outcomes are similar with nebulizer or metered-dose inhaler with valved holding chamber.[48] However, the patient may reject the metered-dose inhaler in favor of the nebulizer. Although that may contradict the clinician's bias, the patient's choice should be respected; moreover, the nebulizer may result in better compliance if it better meets patient expectations.

Evidence-based medicine is not "cookbook" medicine or "cost-cutting" medicine. The best evidence needs extrapolation to the patient's unique pathophysiology and values. With evidence-based medicine, costs may increase, decrease, or remain unchanged.

Hierarchy of Evidence

It has been suggested that a hierarchy of evidence can be used to assess the strength of evidence upon which clinical decisions are based (Table 1).[42,49] The hierarchy implies a clear course of action when addressing a clinical problem. Clinicians should seek the highest available evidence from this hierarchy. Note that evidence always exists but it may be weak. The strongest available evidence may be the unsystematic observations of a single clinician or a generalization from physiologic studies (eg, animal studies or bench studies). Nonetheless, there is always evidence.

Randomization is an important attribute of higher-level evidence. The highest evidence level is an "*n*-of-1" randomized, controlled trial, in which a patient undergoes pairs of treatment periods in which he or she receives a target treatment in one period of each pair and a placebo or alternative in the other.[50–54] The order of the target and control treatment periods is randomized and quantitative ratings are made for each treatment. The *n*-of-1 randomized, controlled trial continues until both the patient and clinician conclude that there is or is not benefit from the intervention. For example, imagine that a decision is made to try positive expiratory pressure therapy with a cystic fibrosis patient. The clinician and patient agree that a clinically useful outcome measure is sputum production. A 12-week trial is designed. For the first week the only sputum clearance technique is huff coughing. For the second week the patient uses huff coughing plus a positive expiratory pressure device (using the technique described by the device manufacturer). In the third week the positive expiratory pressure device is used, but the pressure is set at such a low level that it is probably sub-therapeutic (ie, sham therapy). The patient is naive to the therapy and does not know whether the device should be used with or without the high-pressure setting. The order of treatments is randomized (the patient flips a coin) and the sequence is repeated 4 times. Each day the sputum produced during the therapy session is weighed. A diary is kept in which events such as chest infections are logged. At the end of 12 weeks the results are analyzed (this may include statistical analysis), reviewed together by the clinician and patient, and a collaborative decision is made regarding the benefit of the therapy. In this manner an objective decision is made regarding the benefits of the therapy for this individual patient.

Table 1. Hierarchy of Evidence

Strength of Evidence	Type of Evidence
Strongest	*n*-of-1 randomized trials
	Meta-analysis of randomized trials
	Randomized controlled trials
Intermediate	Systematic reviews of observational studies
	Observational studies
	Physiologic studies
Weakest	Unsystematic clinical observations

There are some therapies for which there has not been a randomized trial and one might argue that a randomized trial is either unethical or unnecessary. For example, it is unlikely that a randomized trial will ever be conducted to study the survival benefit of mechanical ventilation in patients with apnea, transfusion for massive blood loss, or antibiotics for bacterial pneumonia.

In respiratory care some therapies are unproven. In other words, the evidence to support their use is weak. Because a therapy is unproven does not mean that it is wrong, but it also does not mean that is right. There is also the issue of the role, if any, for rescue therapy. Rescue therapy is use of an unproven therapy for a patient who, in the clinical opinion of those providing care, is failing conventional therapy. If the patient improves, that improvement is attributed to the new therapy. Although the majority of patients who receive the rescue therapy do not survive, the survival of the few is attributed to the rescue therapy, which is a most curious reasoning. One might argue that the rescue therapy is ineffective because the majority of patients who receive it do *not* survive (perhaps those with a high likelihood of a good outcome survive in spite of the rescue therapy rather than because of it!). Of concern is that *rescue therapy* is often also *expensive therapy*.

Table 2. Results of a PubMed Search Limited to the Dates of 1/1/2000 to 9/1/2003, Human Studies, and English Language*

Topic	Citations
Mechanical ventilation	2,540
Oxygen therapy	526
Aerosol therapy	1,216
Airway clearance	65
Chronic obstructive pulmonary disease	1,981
Asthma	4,530
Acute respiratory distress syndrome	610
Ventilator-associated pneumonia	134

*It is difficult for any one person to read all of this literature and assess its validity.

Finding the Evidence

There are many sources of evidence. Textbooks are ineffective sources of evidence because the information they contain is often outdated. That is not to say that textbooks are not useful. In fact, they are useful as a source of background information on anatomy, physiology, and pharmacology. A textbook is a good source for students to find large amounts of factual information. However, textbooks generally are not good sources of best evidence. A PubMed search (http://www.pubmed.gov) is an inefficient method of finding the best evidence, because it usually returns an overwhelming amount of information (Table 2). A comprehensive PubMed search for purposes of identifying the best evidence is overwhelming. Few individuals will have the time to read all of the reports identified in a PubMed search, assess the validity of the evidence, and develop strategies to incorporate it into everyday practice.

The efficient approach to finding the best evidence is to identify a systematic review or evidence-based clinical practice guidelines.[55] A systematic review is a summary of the literature that (1) uses explicit methods, (2) is based on a thorough literature search, (3) performs a critical appraisal of individual studies, and (4) uses statistical techniques to combine data from valid studies (meta-analysis).[56] In a systematic review the primary evidence is rigorously identified and appraised. Unlike the traditional narrative review, a systematic review uses explicit methods. In the traditional narrative review the author's bias is stated and supported with a reference (or sometimes a lot of references). A systematic review critically assesses all of the evidence and then bases the review on the strength of that evidence. Systematic reviews have recently become available for the topics of aerosol-delivery-device selection,[48] managing COPD exacerbations,[45] incentive spirometry,[57] airway clearance techniques,[58] and patient selection for noninvasive positive-pressure ventilation.[46,47,59]

Table 3. Grading Schemes Used in Clinical Practice Guidelines

American Association for Respiratory Care grading scheme for evidence-based clinical practice guidelines[61]
- Level 1: Randomized controlled trial with statistically significant results
- Level 2: Randomized controlled trial with substantial threats to validity (eg, small sample size, inappropriate blinding, weak methodology)
- Level 3: Observational study with a concurrent control group
- Level 4: Observational study with a historical control group
- Level 5: Bench study, animal study, case series

Centre for Evidence-Based Medicine (Oxford, United Kingdom) evidence levels[62]
- Level 1a: Systematic review with homogeneity of randomized controlled trials
- Level 1b: Individual randomized controlled trial with narrow confidence interval
- Level 1c: Case series where all patients died before the therapy became available, but some now survive with it; or when some patients died before the therapy became available, but none now die with it
- Level 2a: Systematic review with homogeneity of cohort studies
- Level 2b: Individual cohort study (including low-quality randomized controlled trials)
- Level 2c: Audit or outcomes research
- Level 3a: Systematic review with homogeneity of case-control studies
- Level 3b: Individual case-control study
- Level 4: Case series and poor-quality cohort and case-control studies
- Level 5: Expert opinion without explicit critical appraisal, or based on physiology or bench research

Increasingly, evidence-based clinical practice guidelines are becoming available. Creating an evidence-based guideline requires asking relevant questions, systematically searching the literature, using explicit methodology, grading the evidence, making recommendations, and grading the recommendations based on the strength of the evidence.[60] Table 3 describes 2 examples of recommendation-grading schemes.[61,62] The recommendations must be supported by evidence, and the evidence level must be unambiguous and defensible. If evidence-based guidelines are to be useful, they must be valid. Following are criteria for valid evidence-based guidelines:[42,43]

- Are the recommendations based on a comprehensive review of the literature?
- Is there a systematic review of the literature that is linked to each recommendation?
- Do the recommendations consider all appropriate patient groups?
- Is the strength of each recommendation graded?

		Reference Standard	
		Positive	Negative
Test Result	Positive	a	b
	Negative	c	d

True positive = a
False positive = b
True negative = d
False negative = c
Sensitivity = a/(a + c)
Specificity = d/(b + d)
Likelihood ratio for positive test (LR+) = sensitivity/(1 – specificity)
Likelihood ratio for negative test (LR–) = (1 – sensitivity)/specificity
Positive predictive value (PPV) = a/(a + b)
Negative predictive value (NPV) = d/(c + d)
Diagnostic accuracy = (a + d)/(a + b + c + d)

Converting Between Probability and Odds
Pre-test odds = pre-test probability/(1 – pre-test probability)
Post-test odds = pre-test odds × likelihood ratio
Post-test probability = post-test odds/(post-test odds + 1)

Example: Comparison of the results of a diagnostic test (f/V_T) with the results of a reference standard (successful weaning), assuming that $f/V_T < 100$ indicates weanability.

		Weaning Trial	
		Successful	Unsuccessful
f/V_T	< 100	32	12
	> 100	1	19

True positive = 32
False positive = 12
True negative = 19
False negative = 1
Sensitivity = 32/(32+1) = 97%
Specificity = 19/(12+19) = 61%
Likelihood ratio for positive test (LR+) = 0.97/(1 – 0.61) = 2.49
Likelihood ratio for negative test (LR–) = (1 – 0.97)/0.61 = 0.05
Positive predictive value (PPV) = 32/(32 + 12) = 0.73
Negative predictive value (NPV) = 19/(1 + 19) = 0.95
Diagnostic accuracy = 51/64 = 0.80

Fig. 1. Statistical tests commonly used to assess a diagnostic test. f/V_T = ratio of respiratory frequency to tidal volume (rapid shallow breathing index). (Data adapted from References 66 and 67.)

Recent evidence-based clinical practice guidelines address discontinuation of mechanical ventilation,[63] care of the ventilator circuit and its relation to ventilator-associated pneumonia,[61] sedation,[64] and neuromuscular blockade[65] of mechanically ventilated patients.

Several sources can be searched for evidence-based systematic reviews and clinical practice guidelines. PubMed can be searched with the term "meta-analysis" or "practice guideline." OVID can be searched using the databases "Clinical Evidence," "EBM Reviews - ACP Journal Club," "EBM Reviews - Cochrane Central Register of Controlled Trials," "EBM Reviews - Cochrane Database of Systematic Reviews," "EBM Reviews - Database of Abstracts of Reviews of Effects," and "EBM Reviews Full Text - Cochrane DSR, ACP Journal Club, and DARE."

OVID is a relatively expensive subscription database and is available in many medical libraries. The Cochrane Database is a rich source of systematic reviews, including many related to respiratory care. Abstracts in the Cochrane Database can be searched free of charge (http://www.cochrane.org/reviews/index.htm). Systematic reviews and guidelines may be outdated and should be supplemented by subsequent randomized, controlled trials.

Examining the Evidence for a Diagnostic Test

In respiratory care, diagnostic tests are commonly used to make clinical decisions. Using the tools of evidence-based medicine, metrics are calculated, such as sensitivity, specificity, receiver operating characteristic curves, and likelihood ratios (Fig. 1),[42] which are defined as follows:

Sensitivity: the proportion of patients who have the disorder and are correctly identified by the test

Specificity: the proportion of patients who are free of the disorder and are correctly identified by the test

Likelihood ratio: the relative likelihood that a diagnostic test would be expected in a patient with a disorder of interest (as opposed to one without):

- A likelihood ratio of 1 indicates that the post-test probability is exactly the same as the pre-test probability. Thus, a diagnostic test with an LR of 1 is not helpful.
- A likelihood ratio >1 increases the probability that the target condition is present, and a likelihood ratio <1 decreases the probability that the target condition is present.
- A likelihood ratio >10 or < 0.1 generates large and conclusive changes in the probability of a given diagnosis.
- A likelihood ratio in the range of 5 to 10 or 0.1 to 0.2 generates a moderate and usually useful shift in pre-test to post-test probability.
- A likelihood ratio in the range of 2 to 5 or 0.5 to 0.2 generates a small but sometimes important change in pre-test probability.
- A likelihood ratio in the range of 1 to 2 or 0.5 to 1.0 alters the probability of a given condition to a small and rarely important degree.

Receiver operating characteristic curve: a type of figure that shows the power of a diagnostic test. It plots the true-positive rate (sensitivity) on the vertical axis and the false-positive rate (1-specificity) on the horizontal axis, for different cut-points, thus dividing a positive from a negative test. For a perfect test the area under the curve is 1.0. For a test that performs no better than chance, the area under the curve is 0.5.

The rapid-shallow breathing index (RSBI, which is the ratio of respiratory frequency to tidal volume [f/V_T]) can illustrate the use of these statistical metrics (see Fig. 1).[66] From the data originally published by Yang and Tobin,[67] it can be seen that the likelihood ratio for a positive test

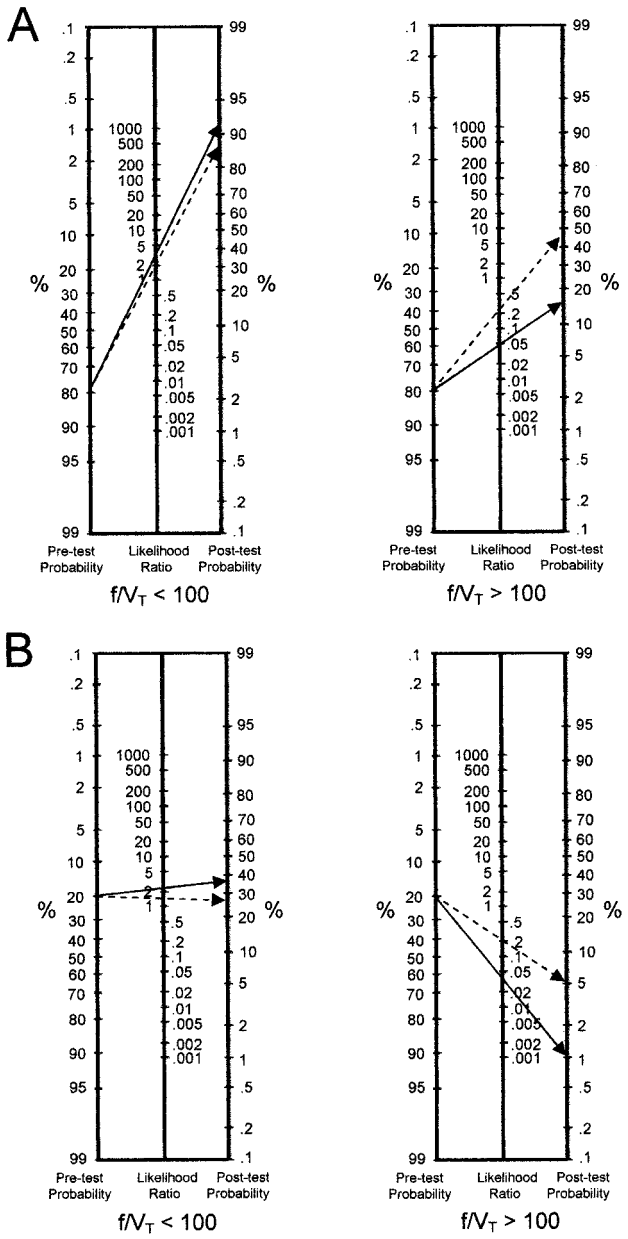

Fig. 2. Use of a nomogram to determine post-test probability from pre-test probability and likelihood ratio. The solid lines represent the likelihood ratio from the report by Yang and Tobin.[67] The dashed line represents the likelihood ratio from the report by Meade et al.[68] A: Patient recovering from ARDS with 80% pre-test probability of weaning. B: Patient recovering from COPD with 20% pre-test probability of weaning. f/V_T = ratio of respiratory frequency to tidal volume (rapid shallow breathing index).

indicating extubation readiness (ie, RSBI $<$ 100) is 2.49 and the likelihood ratio for a negative test (ie, RSBI $>$100) is 0.05. A meta-analysis by Meade et al[68] suggests likelihood ratios of 1.58 for positive and 0.22 for negative predictions. Likelihood ratios of those magnitudes generate a small change in pre-test probability.

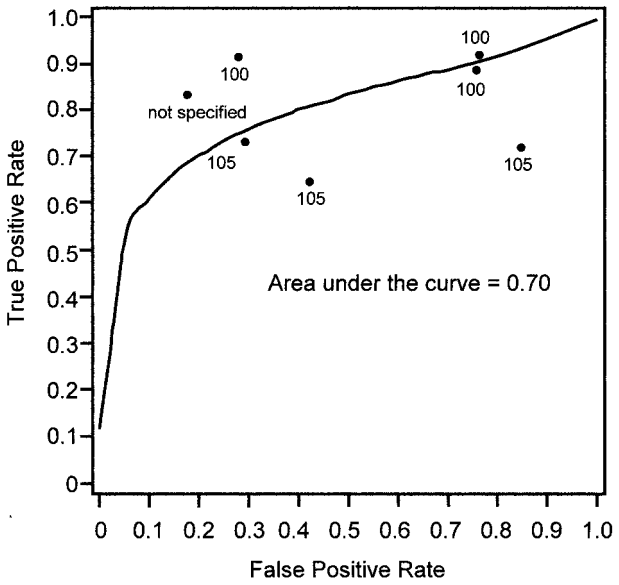

Fig. 3. Summary receiver operating characteristic curve for the ability of the rapid shallow breathing index (RSBI, which is the ratio of respiratory frequency to tidal volume) to predict successful extubation. The numbers in the figure represent the RSBI cut points from the various studies. (Adapted from Reference 68.)

A nomogram can be used to derive post-test probabilities from the pre-test probability and the likelihood ratio.[69] Imagine a 25-year-old patient with resolving ARDS following multiple trauma. In your experience 80% of similar patients extubate successfully following resolution of the ARDS (ie, the pre-test probability of successful extubation is 80%). Suppose that the patient's RSBI is 85 (breaths/min)/L (test positive for extubation). As shown in Figure 2, using the likelihood ratio from either Yang and Tobin[67] or Meade et al[68] produces a post-test probability of successful extubation that differs little from the pre-test probability. However, if the RSBI is 120 (breaths/min)/L (test negative for extubation), the post-test probability of successful extubation does change—particularly with the likelihood ratio from Yang and Tobin.[67]

Imagine a 75-year-old patient with resolving COPD exacerbation. In your experience only 20% of similar patients extubate successfully following resolution of the COPD exacerbation (ie, pre-test probability of successful extubation is 20%). Suppose the patient's RSBI is 85 (breaths/min)/L. As shown in Figure 2, the likelihood ratio with either Yang and Tobin[67] or Meade et al[68] produces a post-test probability of successful extubation that increases the pre-test probability, but not by a lot. However, if the RSBI is 120 (breaths/min)/L the post-test probability of successful extubation is extremely low, particularly with the likelihood ratio from Yang and Tobin.[67]

The previous examples not only illustrate how the tools of evidence-based medicine can be applied to a diagnostic

test but also that the diagnostic tests that have come into common use (eg, RSBI) may marginally affect post-test probability and thus clinical decision-making. This can also be illustrated with the receiver operating characteristic curve (Fig. 3). The modest area under the curve (0.70) indicates that the RSBI has no more than modest accuracy for predicting extubation readiness.[68]

Examining the Evidence for a Therapy

Increasingly, studies are being published related to respiratory therapy. It is important to assess the validity of such studies. High-level studies are prospective, randomized, blinded, placebo-controlled, concealed allocation, parallel design, and assess patient-important outcomes.[42]

Prospective study: prospective investigation of the factors that might cause a disorder in which a cohort of individuals who do not have evidence of the outcome of interest but who have been exposed to the putative cause are compared with a concurrent cohort who are also free of the outcome but have not been exposed to the putative cause. Both cohorts are then followed to compare the incidence of the outcome of interest.

Randomization: random allocation of individuals to study groups, usually done with the aid of a table of random numbers. This differs from systematic allocation (eg, even and odd days of the month) or allocation at the convenience or discretion of the investigator.

Blind (or *blinded* or *masked*): The research participant of interest (the patient, the clinician, the person monitoring outcomes, the assessor of outcomes, the data analyst, and/or and the person who writes the report) is unaware of whether the patient has been assigned to the experimental group or control group.

Placebo: intervention without biologically active attributes

Concealment: Randomization is concealed if the person who is making the decision about enrolling a patient is unaware of whether the next patient enrolled will be entered in the treatment or control group.

Parallel design: Subjects are randomly assigned to the treatment or control group, an intervention is applied, and the outcome is identified for each subject. This is different than a cross-over study, in which subjects receive both the treatment and the control intervention.

Depending on the type of study, some of the latter research principles cannot be applied. For example, blinding is not possible with studies of aerosol-delivery devices. Placebo-controlled studies of noninvasive ventilation are difficult to implement.

When assessing a therapy, it is important to evaluate a patient-important outcome. Clinicians are often interested in physiologic outcomes such as arterial blood gas values. Patients, on the other hand, are more interested in outcomes such as survival. There are situations in which an improvement in a physiologic variable such as P_{aO_2} does not correlate with patient-important outcomes. For ARDS patients inhaled nitric oxide improves P_{aO_2} but not mortality.[70] Mask CPAP improves P_{aO_2} but not intubation rate or mortality.[71] For ARDS patients prone positioning improves P_{aO_2} but not mortality.[72] With ARDS patients higher V_T improves P_{aO_2} but mortality is lower with lower V_T.[44]

		Outcome	
		Present	Absent
Treatment	Present	a	b
	Absent	c	d

Controlled event rate (CER) = c/(c + d)
Experimental event rate (EER) = a/(a + b)
Relative risk (RR) = EER/CER = [a/(a + b)]/[c/(c + d)]
Relative risk reduction (RRR) = 1 – RR
Absolute risk reduction (ARR) = c/(c + d) – a/(a + b)
Number needed to treat (NNT) = 1/ARR
Odds ratio (OR) = (a × d)/(c × b)

Example: The results of the ARDS Network study.[44]

		Outcome	
		Dead at 28 d	Alive at 28 d
Treatment	V_T of 6 mL/kg	134	298
	V_T of 12 mL/kg	171	259

Control-group (12 mL/kg) mortality = 171/(171 + 259) = 0.398
Experimental-group (6 mL/kg) mortality = 134/(134 + 298) = 0.31
Relative risk (RR) = 0.31/0.398 = 0.787
Relative risk reduction = 1 – 0.787 = 0.213 (21.3%)
Absolute risk reduction = 0.398 – 0.31 = 0.088 (8.8%)
Number needed to treat = 1/0.088 = 11
Odds ratio = (134 × 259)/(171 × 298) = 0.68

Fig. 4. Statistical tests commonly used to assess a therapy.

Using the tools of evidence-based medicine, metrics can be calculated, such as event rate, relative risk, relative risk reduction, absolute risk reduction, number needed to treat, and odds ratio (Figure 4),[42] which are defined as follows:

Event rate: proportion of patients in a group in whom an event is observed. "Control event rate" and "experimental event rate" refer to the event rates in the control and experimental groups.

Relative risk: ratio of the risk of an event in the experimental group to the risk in the control group. A relative risk < 1 indicates benefit from the intervention, a relative risk > 1 indicates harm from the intervention, and a relative risk $= 1$ means the intervention has no effect.

Relative risk reduction: estimate of the proportion of baseline risk that is removed by the therapy.

Absolute risk reduction: difference in the absolute risk (percentage or proportion of patients with an outcome) in the exposed (experimental event rate) versus the unexposed (control event rate).

Number needed to treat: number of patients who need to be treated to prevent one bad outcome

Odds ratio: ratio of the odds of an event in an exposed group to the odds of the same event in a group that is not exposed

Another important statistic used in evidence-based medicine is the confidence interval, which is defined as the range of values within which it is probable that the true value lies for the whole population of patients from whom the study patients were selected. The confidence interval is affected by sample size and effect size (ie, the difference in outcomes between the intervention and control groups divided by some measure of variability, typically the standard deviation). The confidence interval draws attention to the importance of sample size. A larger sample size narrows the range of the confidence interval, increasing the precision of the study results. A larger sample size also decreases the risk of a type 2 (or beta) error, in which the study fails to detect a statistically significant difference between the treatment and control groups. High-level studies conduct a power analysis as part of the study design so that an appropriate sample size can be determined a priori.

The ARDS Network study provides an example.[44] In that study 861 patients with ARDS or acute lung injury (ALI) were randomly assigned to be mechanically ventilated with a V_T of either 12 mL/kg or 6 mL/kg. The primary outcome was mortality. Figure 4 shows the relevant statistics. The mortality of the control group (12 mL/kg) was 39.8% and the mortality of the treatment group (6 mL/kg) was 31%. The relative risk of mortality was lower in the treatment group (0.787), with a relative risk reduction of 0.213 compared to the control group. For mortality there was an absolute risk reduction of 8.8%, resulting in a number-needed-to-treat of 11 patients. In other words, for every 11 mechanically ventilated patients with ALI or ARDS who receive a V_T of 6 mL/kg (rather than 12 mL/kg) 1 additional life will be saved.

Meta-Analysis

Meta-analysis is a statistical analysis that combines the results of several independent studies.[42] As with any study design, the question asked will influence the design and the method of meta-analysis. Since it is based on a literature review, the meta-analysis is observational rather than experimental in nature. The person conducting the meta-analysis has limited control over the availability of studies or the information reported in individual studies. The studies included in the meta-analysis should be comparable, but the degree of comparability is subjective and determined by the person conducting the meta-analysis. Included studies should be identified from a comprehensive review of the literature, and unpublished data should ideally be included to reduce the risk of publication bias. Clinical trials related to respiratory care are often expensive, and it may be difficult to recruit an adequate sample size to avoid a beta error. A meta-analysis uses statistical methods to combine the results of several studies into a single pooled metric. As seen in Table 1, a meta-analysis of randomized, controlled trials is a higher level of evidence than a single randomized, controlled trial. The results of a meta-analysis are often displayed as a "forest plot" (Fig. 5). Meta-analyses of various respiratory-care-related topics have recently been published, including ventilator circuit change intervals,[61] lung-protective ventilation strategies,[73] continuous aerosol bronchodilator administration,[74] the therapeutic values of helium-oxygen mixture,[75] and high-frequency ventilation of neonates.[76]

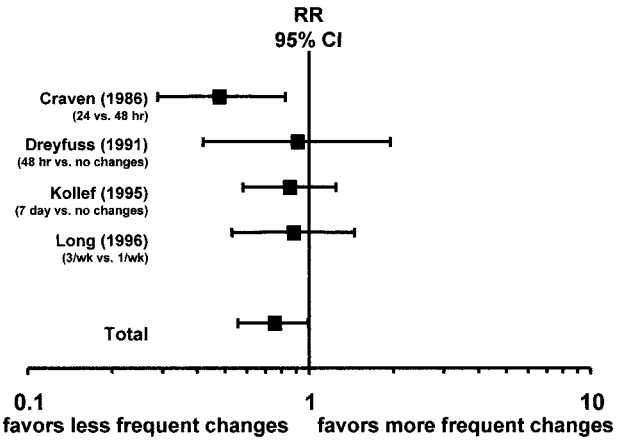

Fig. 5. An example of a forest plot, as used to display meta-analysis results. Shown are the relative risk (RR) point estimates and 95% confidence intervals (CIs) from the individual studies and from the pooled meta-analysis (total). In this example the RR for ventilator-associated pneumonia is lower with less frequent ventilator circuit changes. (From Reference 61).

Why Isn't the Best Evidence Implemented Into Practice?

The tenets of evidence-based medicine are not universally accepted. Some clinicians do not accept a hierarchy of evidence, arguing instead that experiential evidence and evidence from physiologic trials is as important as, or perhaps even more important than, empirical evidence from well-done prospective randomized trials with humans.[77,78] It is often pointed out that high-level evidence does not exist for many respiratory care practices. However, that is no excuse for not implementing high-level evidence when it is available. Evidence-based medicine does not discredit the value of physiologic studies. Such studies are important to assess mechanisms of disease and to establish proof of principle. Studies lower on the hierarchy of evidence should not be ignored. However, physiologic studies should impact clinical practice less than the results of a well-done randomized, controlled trial.

The ARDS Network study[44] is a case in point. Despite the strength of the ARDS Network finding that mortality is lower with a V_T of 6 mL/kg than with 12 mL/kg, some well-intentioned clinicians nonetheless reject that finding.[79] One recent study reported minimally reduced V_T in teaching hospitals for the 2 years following publication of the ARDS Network findings.[80] I have heard a number of arguments for not following the ARDS Network protocol:

- "They used volume-controlled ventilation and I like pressure control."
- "Patients don't look good when we try that."
- "They didn't use enough PEEP [positive end-expiratory pressure] and they did not perform recruitment maneuvers."
- "How do I know that 6 mL/kg is correct when they didn't study other V_T between 6 and 12 mL/kg?"

These arguments are curious, given that the ARDS Network study provides the best evidence to date regarding ventilator settings for ALI and ARDS patients. And subsequent studies by the ARDS Network have not found a physiologic benefit from recruitment maneuvers[81] or a survival benefit for higher PEEP.[82] The benefit in terms of patient-important outcomes (mortality) seems to be from limiting volume and pressure. There have also been modifications to the ARDS Network protocol in everyday practice. Some have interpreted the ARDS Network findings to mean that the V_T is not important, provided that the plateau pressure is < 30 cm H_2O.[78] However, this is not how the ARDS Network protocol was implemented in the randomized trial. If one is to expect outcomes comparable to those reported in the randomized trial, then the treatment must be implemented the same way: same dose (6 mL/kg), same dosing algorithm (V_T based on predicted body weight), same dosing strategy (volume-controlled ventilation), same patient population (ALI and ARDS), same adjunctive therapy (PEEP-F_{IO_2} ladder). Perhaps some of these aspects are not important to the implementation of the ARDS Network protocol. Maybe pressure control can be used instead of volume control. But we don't know; that study has not been done. Caution should be taken to avoid contaminating the evidence with local bias.

Another example relevant to respiratory care practice is the use of semirecumbent position with mechanically ventilated patients. Randomized trials have shown that with mechanically ventilated patients the semirecumbent position is associated with less aspiration and pneumonia than the supine position.[83–86] Despite evidence of better outcomes with this inexpensive intervention, semirecumbent positioning is underutilized. Interestingly, one study reported that nurses thought the primary obstacle to use of semirecumbency was physicians' orders, whereas physicians thought the main obstacle was nursing preference.[87] Unfortunately, blaming is a common barrier to the implementation of evidence-based practice. Table 4 list some reasons evidence-based practice is not implemented.

Table 4. Common Reasons Clinicians Do Not Practice Evidence-Based Medicine

They do not recognize the evidence (laziness)
They do not read the literature
They do not attend conferences
They do not talk to their colleagues
They do not believe the evidence (ignorance)
They do not believe the right study was done (eg, wrong dose)
The study is not consistent with lower levels of evidence (eg, animal studies)
They believe that incorporating the evidence into practice is someone else's job (blaming)
The system prevents incorporating the latest evidence
There is not enough time
The right resources are not available
There is not hospital policy supporting the practice change
They do not think the evidence applies to their practice (stubbornness)
Their patients are sicker
Their patients are older
Their patients have always done fine with their "expert" treatment

There is also the example of hand hygiene. All clinicians know that hand cleansing is important to prevent the spread of infection. Compliance with this practice, however, is embarrassingly low. A study by Harbarth et al[88] reported that the average hand hygiene compliance was 68% among respiratory therapists, 37% among physicians, and 29% among nurses. Despite the convenience of effective hand-rubbing aqueous alcohol solutions strategically placed throughout the patient care areas of the hospital, compliance with the evidence-based practice of hand cleansing is pathetic.

Summary

Evidence-based medicine has permeated all parts of health care practice, including respiratory care. The principles of evidence-based medicine provide us the tools to incorporate the best evidence into our everyday practice. Although not all tenets of evidence-based medicine are universally accepted, the principles of evidence-based medicine nonetheless provide a valuable approach to improve respiratory care practice.

REFERENCES

1. Evidence-Based Medicine Working Group. Evidence-based medicine: a new approach to teaching the practice of medicine. JAMA 1992;268(17):2420–2425.

2. Guyatt GH, Haynes RB, Jaeschke RZ, Cook DJ, Green L, Naylor CD, et al. Users' guides to the medical literature: XXV. Evidence-based medicine: principles for applying the users' guides to patient care. Evidence-Based Medicine Working Group. JAMA 2000; 284(10):1290–1296.
3. Richardson WS, Wilson MC, Williams JW Jr, Moyer VA, Naylor CD. Users' guides to the medical literature: XXIV. How to use an article on the clinical manifestations of disease. Evidence-Based Medicine Working Group. JAMA 2000;284(7):869–875.
4. Giacomini MK, Cook DJ. Users' guides to the medical literature: XXIII. Qualitative research in health care B. What are the results and how do they help me care for my patients? Evidence-Based Medicine Working Group. JAMA 2000;284(4):478–482.
5. Giacomini MK, Cook DJ. Users' guides to the medical literature: XXIII. Qualitative research in health care A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA 2000; 284(3):357–362.
6. McGinn TG, Guyatt GH, Wyer PC, Naylor CD, Stiell IG, Richardson WS. Users' guides to the medical literature: XXII: how to use articles about clinical decision rules. Evidence-Based Medicine Working Group. JAMA 2000;284(1):79–84.
7. McAlister FA, Straus SE, Guyatt GH, Haynes RB. Users' guides to the medical literature: XX. Integrating research evidence with the care of the individual patient. Evidence-Based Medicine Working Group JAMA 2000;283(21):2829–2836.
8. Hunt DL, Jaeschke R, McKibbon KA. Users' guides to the medical literature: XXI. Using electronic health information resources in evidence-based practice. Evidence-Based Medicine Working Group. JAMA 2000;283(14):1875–1879.
9. Bucher HC, Guyatt GH, Cook DJ, Holbrook A, McAlister FA. Users' guides to the medical literature: XIX. Applying clinical trial results. A. How to use an article measuring the effect of an intervention on surrogate end points. Evidence-Based Medicine Working Group. JAMA 1999;282(8):771–778.
10. Barratt A, Irwig L, Glasziou P, Cumming RG, Raffle A, Hicks N, et al. Users' guides to the medical literature: XVII. How to use guidelines and recommendations about screening. Evidence-Based Medicine Working Group. JAMA 1999;281(21):2029–2034.
11. Guyatt GH, Sinclair J, Cook DJ, Glasziou P. Users' guides to the medical literature: XVI. How to use a treatment recommendation. Evidence-Based Medicine Working Group and the Cochrane Applicability Methods Working Group. JAMA 1999;281(19):1836–1843.
12. Richardson WS, Wilson MC, Guyatt GH, Cook DJ, Nishikawa J. Users' guides to the medical literature: XV. How to use an article about disease probability for differential diagnosis. Evidence-Based Medicine Working Group. JAMA 1999;281(13):1214–1219.
13. Dans AL, Dans LF, Guyatt GH, Richardson S. Users' guides to the medical literature: XIV. How to decide on the applicability of clinical trial results to your patient. Evidence-Based Medicine Working Group. JAMA 1998;279(7):545–549.
14. O'Brien BJ, Heyland D, Richardson WS, Levine M, Drummond MF. Users' guides to the medical literature: XIII. How to use an article on economic analysis of clinical practice. B. What are the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. JAMA 1997;277(22):1802–1806. Erratum in: JAMA 1997;278(13):1064.
15. Drummond MF, Richardson WS, O'Brien BJ, Levine M, Heyland D. Users' guides to the medical literature. XIII. How to use an article on economic analysis of clinical practice. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA 1997; 277(19):1552–1557.
16. Guyatt GH, Naylor CD, Juniper E, Heyland DK, Jaeschke R, Cook DJ. Users' guides to the medical literature. XII. How to use articles about health-related quality of life. Evidence-Based Medicine Working Group. JAMA 1997;277(15):1232–1237.
17. Naylor CD, Guyatt GH. Users' guides to the medical literature. XI. How to use an article about a clinical utilization review. Evidence-Based Medicine Working Group. JAMA 1996;275(18):1435–1439.
18. Naylor CD, Guyatt GH. Users' guides to the medical literature. X. How to use an article reporting variations in the outcomes of health services. The Evidence-Based Medicine Working Group. JAMA 1996;275(7):554–558.
19. Guyatt GH, Sackett DL, Sinclair JC, Hayward R, Cook DJ, Cook RJ. Users' guides to the medical literature. IX. A method for grading health care recommendations. Evidence-Based Medicine Working Group. JAMA 1995;274(22):1800–1804. Erratum in: JAMA 1996; 275(16):1232.
20. Wilson MC, Hayward RS, Tunis SR, Bass EB, Guyatt G. Users' guides to the medical literature. VIII. How to use clinical practice guidelines. B. What are the recommendations and will they help you in caring for your patients? The Evidence-Based Medicine Working Group. JAMA 1995;274(20):1630–1632.
21. Hayward RS, Wilson MC, Tunis SR, Bass EB, Guyatt G. Users' guides to the medical literature. VIII. How to use clinical practice guidelines. A. Are the recommendations valid? The Evidence-Based Medicine Working Group. JAMA 1995;274(7):570–574.
22. Richardson WS, Detsky AS. Users' guides to the medical literature. VII. How to use a clinical decision analysis. B. What are the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. JAMA 1995;273(20):1610–1613.
23. Richardson WS, Detsky AS. Users' guides to the medical literature. VII. How to use a clinical decision analysis. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA 1995; 273(16):1292–1295.
24. Oxman AD, Cook DJ, Guyatt GH. Users' guides to the medical literature. VI. How to use an overview. Evidence-Based Medicine Working Group. JAMA 1994;272(17):1367–1371.
25. Laupacis A, Wells G, Richardson WS, Tugwell P. Users' guides to the medical literature. V. How to use an article about prognosis. Evidence-Based Medicine Working Group. JAMA 1994;272(3):234–237.
26. Levine M, Walter S, Lee H, Haines T, Holbrook A, Moyer V. Users' guides to the medical literature. IV. How to use an article about harm. Evidence-Based Medicine Working Group. JAMA 1994; 271(20):1615–1619.
27. Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. JAMA 1994;271(9):703–707.
28. Jaeschke R, Guyatt G, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA 1994;271(5):389–391.
29. Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. JAMA 1994; 271(1):59–63.
30. Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA 1993;270(21):2598–2601.
31. Oxman AD, Sackett DL, Guyatt GH. Users' guides to the medical literature. I. How to get started. The Evidence-Based Medicine Working Group. JAMA 1993;270(17):2093–2095.

32. Moseley JB, O'Malley K, Petersen NJ, Menke TJ, Brody BA, Kuykendall DH, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med 2002;347(2):81–88.
33. Pompeo E, Marino M, Nofroni I, Matteucci G, Mineo TC. Reduction pneumoplasty versus respiratory rehabilitation in severe emphysema: a randomized study. Pulmonary Emphysema Research Group. Ann Thorac Surg 2000;70(3):948–953; discussion 954.
34. Cooper JD, Patterson GA, Sundaresan RS, Trulock EP, Yusen RD, Pohl MS, Lefrak SS. Results of 150 consecutive bilateral lung volume reduction procedures in patients with severe emphysema. J Thorac Cardiovasc Surg 1996;112(5):1319–1329; discussion 1329–1330.
35. Criner GJ, Cordova FC, Furukawa S, Kuzma AM, Travaline JM, Leyenson V, O'Brien GM. Prospective randomized trial comparing bilateral lung volume reduction surgery to pulmonary rehabilitation in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;160(6):2018–2027.
36. Flaherty KR, Kazerooni EA, Curtis JL, Iannettoni M, Lange L, Schork MA, Martinez FJ. Short-term and long-term outcomes after bilateral lung volume reduction surgery: prediction by quantitative CT. Chest 2001;119(5):1337–1346.
37. Geddes D, Davies M, Koyama H, Hansell D, Pastorino U, Pepper J, et al. Effect of lung-volume-reduction surgery in patients with severe emphysema. N Engl J Med 2000;343(4):239–245.
38. Sciurba FC, Rogers RM, Keenan RJ, Slivka WA, Gorcsan J 3rd, Ferson PF, et al. Improvement in pulmonary function and elastic recoil after lung-reduction surgery for diffuse emphysema. N Engl J Med 1996;334(17):1095–1099.
39. Brenner M, Yusen R, McKenna R Jr, Sciurba F, Gelb AF, Fischel R, et al. Lung volume reduction surgery for emphysema. Chest 1996; 110(1):205–218.
40. Gelb AF, McKenna RJ Jr, Brenner M, Schein MJ, Zamel N, Fischel R. Lung function 4 years after lung volume reduction surgery for emphysema. Chest 1999;116(6):1608–1615.
41. Fishman A, Martinez F, Naunheim K, Piantadosi S, Wise R, Ries A, et al; National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume–reduction surgery with medical therapy for severe emphysema. N Engl J Med 2003;348(21): 2059–2073.
42. Guyatt G, Drummond R. Users' guides to the medical literature: a manual for evidence-based clinical practice. Chicago: AMA Press; 2002.
43. Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB. Evidence-based medicine: how to practice and teach EBM. New York: Churchill Livingstone; 2000.
44. 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.
45. McCrory DC, Brown C, Gelfand SE, Bach PB. Management of acute exacerbations of COPD: a summary and appraisal of published evidence. Chest 2001;119(4):1190–1209.
46. Keenan SP, Sinuff T, Cook DJ, Hill NS. Which patients with acute exacerbation of chronic obstructive pulmonary disease benefit from noninvasive positive-pressure ventilation? A systematic review of the literature. Ann Intern Med 2003;138(11):861–870.
47. Lightowler JV, Wedzicha JA, Elliott MW, Ram FSF. Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. BMJ 2003;326(7382):185–189.
48. Ram FS, Wright J, Brocklebank D, White JE. Systematic review of clinical effectiveness of pressurised metered dose inhalers versus other hand held inhaler devices for delivering β_2 agonists bronchodilators in asthma. BMJ 2001;323(7318):901–905.
49. Montori VM, Guyatt GH. What is evidenced-based medicine and why should it be practiced? Respir Care 2001;46(11):1201–1214.
50. Guyatt G, Sackett D, Taylor DW, Chong J, Roberts R, Pugsley S. Determining optimal therapy—randomized trials in individual patients. N Engl J Med 1986;314(14):889–892.
51. Mahon JL, Laupacis A, Hodder RV, McKim DA, Paterson NA, Wood TE, Donner A. Theophylline for irreversible chronic airflow limitation: a randomized study comparing n of 1 trials to standard practice. Chest 1999;115(1):38–48.
52. Mahon J, Laupacis A, Donner A, Wood T. Randomised study of n of 1 trials versus standard practice. BMJ 1996;312(7038):1069–1074. Erratum in: BMJ 1996;312(7043):1392.
53. Patel A, Jaeschke R, Guyatt GH, Keller JL, Newhouse MT. Clinical usefulness of n-of-1 randomized controlled trials in patients with nonreversible chronic airflow limitation. Am Rev Respir Dis 1991; 144(4):962–964.
54. Guyatt G, Sackett D, Adachi J, Roberts R, Chong J, Rosenbloom D, Keller J. A clinician's guide for conducting randomized trials in individual patients. CMAJ 1988;139(6):497–503.
55. Doig GS, Simpson F. Efficient literature searching: a core skill for the practice of evidence-based medicine. Intensive Care Med 2003; 29(12):2119–2127.
56. Cook DJ. Moving toward evidence-based practice. Respir Care 2003; 48(9):859–868.
57. Overend TJ, Anderson CM, Lucy SD, Bhatia C, Jonsson BI, Timmermans C. The effect of incentive spirometry on postoperative pulmonary complications: a systematic review. Chest 2001;120(3): 971–978.
58. Hess DR. The evidence for secretion clearance techniques. Respir Care 2001;46(11):1276–1293.
59. Peter JV, Moran JL, Phillips-Hughes J, Warn D. Noninvasive ventilation in acute respiratory failure–a meta-analysis update. Crit Care Med 2002;30(3):555–562.
60. Hess DR. Evidence-based clinical practice guidelines: where's the evidence and what do I do with it? (editorial) Respir Care 2003; 48(9):838–839.
61. American Association for Respiratory Care. AARC Evidence-Based Clinical Practice Guideline: Care of the ventilator circuit and its relation to ventilator-associated pneumonia. Respir Care 2003;48(9): 869–879.
62. Levels of evidence and grades of recommendation. Oxford Centre for Evidence-based Medicine. Available at http://www.cebm.net/levels_of_evidence.asp. Accessed April 27, 2004.
63. MacIntyre NR, Cook DJ, Ely EW Jr, Epstein SK, Fink JB, Heffner JE, et al; American College of Chest Physicians; American Association for Respiratory Care; American College of Critical Care Medicine. Evidence-based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. Chest 2001;120(6 Suppl):375S–395S.
64. Jacobi J, Fraser GL, Coursin DB, Riker RR, Fontaine D, Wittbrodt ET, et al; Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM), American Society of Health-System Pharmacists (ASHP), American College of Chest Physicians. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med 2002;30(1):119–141. Erratum in: Crit Care Med 2002; 30(3):726.
65. Murray MJ, Cowen J, DeBlock H, Erstad B, Gray AW Jr, Tescher AN, et al; Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM), American Society of Health-System Pharmacists, American College of Chest Physicians. Clinical practice guidelines for sustained neu-

romuscular blockade in the adult critically ill patient. Crit Care Med 2002;30(1):142–156.
66. Jaeschke RZ, Meade MO, Guyatt GH, Keenan SP, Cook DJ. How to use diagnostic test articles in the intensive care unit: diagnosing weanability using f/V_T. Crit Care Med 1997;25(9):1514–1521.
67. Yang KL, Tobin MJ. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. N Engl J Med 1991;324(21):1445–1450.
68. Meade M, Guyatt G, Cook D, Griffith L, Sinuff T, Kergl C, et al. Predicting success in weaning from mechanical ventilation. Chest 2001;120(6 Suppl):400S–424S.
69. Fagan TJ. Nomogram for Bayes theorem (letter). N Engl J Med 1975;293(5):257.
70. Dellinger RP, Zimmerman JL, Taylor RW, Straube RC, Hauser DL, Criner GJ, et al. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. Inhaled Nitric Oxide in ARDS Study Group. Crit Care Med 1998; 26(1):15–23.
71. Delclaux C, L'Her E, Alberti C, Mancebo J, Abroug F, Conti G, et al. Treatment of acute hypoxemic nonhypercapnic respiratory insufficiency with continuous positive airway pressure delivered by a face mask: a randomized controlled trial. JAMA 2000;284(18):2352–2360.
72. Gattinoni L, Tognoni G, Pesenti A, Taccone P, Mascheroni D, Labarta V, et al; Prone-Supine Study Group. Effect of prone positioning on the survival of patients with acute respiratory failure. N Engl J Med 2001;345(8):568–573.
73. Brower RG, Rubenfeld GD. Lung-protective ventilation strategies in acute lung injury. Crit Care Med 2003;31(4 Suppl):S312–S316.
74. Rodrigo GJ, Rodrigo C. Continuous vs intermittent β-agonists in the treatment of acute adult asthma: a systematic review with meta-analysis. Chest 2002;122(1):160–165.
75. Rodrigo GJ, Rodrigo C, Pollack CV, Rowe B. Use of helium-oxygen mixtures in the treatment of acute asthma: a systematic review. Chest 2003;123(3):891–896.
76. Bollen CW, Uiterwaal CS, van Vught AJ. Cumulative metaanalysis of high-frequency versus conventional ventilation in premature neonates. Am J Respir Crit Care Med 2003;168(10):1150–1155.
77. Tobin MJ. The role of a journal in a scientific controversy (editorial). Am J Respir Crit Care Med 2003;168(5):511.
78. Tobin MJ. Culmination of an era in research on the acute respiratory distress syndrome (editorial). N Engl J Med 2000;342(18):1360–1361.
79. Eichacker PQ, Gerstenberger EP, Banks SM, Cui X, Natanson C. Meta-analysis of acute lung injury and acute respiratory distress syndrome trials testing low tidal volumes. Am J Respir Crit Care Med 2002;166(11):1510–1514.
80. Weinert CR, Gross CR, Marinelli WA. Impact of randomized trial results on acute lung injury ventilator therapy in teaching hospitals. Am J Respir Crit Care Med 2003;167(10):1304–1309.
81. Brower RG, Morris A, MacIntyre N, Matthay MA, Hayden D, Thompson T, et al; ARDS Clinical Trials Network; National Heart, Lung, and Blood Institute; National Institutes of Health. Effects of recruitment maneuvers in patients with acute lung injury and acute respiratory distress syndrome ventilated with high positive end-expiratory pressure. Crit Care Med 2003;31(11):2592–2597.
82. Brower RG. NHLBI ARDS Network update: ventilatory management protocol (ALVEOLI). Program of the 98th International Conference of the American Thoracic Society. May 17–22, 2002. Atlanta, Georgia. Available at http://www.medscape.com/viewprogram/1930_pnt. Accessed May 3, 2004.
83. Torres A, Serra-Batlles J, Ros E, Piera C, Puig de la Bellacasa J, Cobos A, et al. Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: the effect of body position. Ann Intern Med 1992;116(7):540–543.
84. Ibanez J, Penafiel A, Raurich JM, Marse P, Jorda R, Mata F. Gastroesophageal reflux in intubated patients receiving enteral nutrition: effect of supine and semirecumbent positions. JPEN J Parenter Enteral Nutr 1992;16(5):419–422.
85. Orozco-Levi M, Torres A, Ferrer M, Piera C, el-Ebiary M, de la Bellacasa JP, Rodriguez-Roisin R. Semirecumbent position protects from pulmonary aspiration but not completely from gastroesophageal reflux in mechanically ventilated patients. Am J Respir Crit Care Med 1995;152(4 Pt 1):1387–1390.
86. Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogue S, Ferrer M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. Lancet 1999; 354(9193):1851–1858.
87. Cook DJ, Meade MO, Hand LE, McMullin JP. Toward understanding evidence uptake: semirecumbency for pneumonia prevention. Crit Care Med 2002;30(7):1472–1477.
88. Harbarth S, Pittet D, Grady L, Goldmann DA. Compliance with hand hygiene practice in pediatric intensive care. Pediatr Crit Care Med 2001;2(4):311–314.