Reflecting on Eight Editions of the American College of Chest Physicians Antithrombotic Guidelines

Jack Hirsh, Gordon Guyatt and Sandra Zelman Lewis

*Chest* 2008;133:1293-1295
DOI 10.1378/chest.08-0782

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Reflecting on Eight Editions of the American College of Chest Physicians Antithrombotic Guidelines

The American College of Chest Physicians (ACCP) guidelines addressing antithrombotic therapy, first published in 1986, have been updated about every 3 years. The eighth edition of the guidelines [now called “Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)" is published as a special supplement of CHEST this month. Over the past 2 decades, these guidelines have adapted to trends in evidence-based medicine and helped to raise the standards for guideline methodology. The eighth edition has, judging by the numerous daily requests for the publication date, been one of the most anxiously anticipated products of the ACCP.

This document provides an extensive update of evidence-based guidelines for the management of thromboembolic conditions affecting the venous and arterial systems (including the coronary, cerebral, and peripheral arteries), and the cardiac chambers, including native and prosthetic valves. The guidelines also address the management of thromboembolism in the pediatric population and during pregnancy, the management of patients who are treated with anticoagulants and require bridging therapy because of an intercurrent invasive procedure, and the management of heparin-induced thrombocytopenia. We also include chapters reviewing the pharmacology of the approved anticoagulants (heparin, low-molecular-weight heparins, fondaparinux, hirudin, bivalirudin, and argatroban), antiplatelet drugs (aspirin, clopidogrel, ticlopidine, dipyridamole, and the glycoprotein IIb/IIIa antagonists), and thrombolytic agents (streptokinase, tissue plasminogen activator, and the tissue plasminogen activator analogs tenecteplase and reteplase). These introductory chapters include recommendations for the dosing and monitoring of anticoagulants and antiplatelet agents.

The grading system in the eighth edition of the guidelines has been modified slightly from the previous versions. The grading system in the eighth edition now reflects the system adopted for all ACCP guidelines, similar to the GRADE system, which is being widely adopted by many guideline development organizations. This system provides ratings of the quality of evidence (high quality [A], moderate quality [B], and low quality [C]) and of strength of recommendations based on the balance of risks or burdens to benefits (strong [1] and weak [2]).

Since the initial publication of the guidelines 20 years ago, investigators have made enormous progress in generating high-quality data through well-designed, randomized trials that allow for strong recommendations. Table 1 shows this increase in high-quality evidence, which is reflected in the number of 1A recommendations (referred to as “A1” in earlier publications). Both the total number and the number of 1A recommendations have increased progressively with each publication of the guidelines. The proportion of 1A recommendations has varied between 17% and 25% of the total. The number and diversity of participants in the guideline development panels have also increased over time (Table 2).

We have also improved the scientific rigor of the review process in a number of ways. Each recommendation corresponds to a clearly defined and clearly documented structured research question, and a team of methodologists has conducted a systematic search for relevant evidence. We have standardized

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*The A1 recommendations were referred to as “A1” recommendations in earlier publications of the guidelines.
the criteria for rating the quality of individual randomized trials and observational studies, and the criteria for rating overall quality of evidence and recommendations are increasingly refined and rigorous. Resource allocation has been considered for selected recommendations in several chapters.

Over the iterations of the ACCP thrombosis guidelines, the panelists have become increasingly, and now vividly, aware that values and preferences underlie all recommendations. Whose values and preferences should guide tradeoffs such as those between avoiding thrombotic events and precipitating bleeding? Most would agree that patient and community values should drive the recommendations. That awareness presents a challenge: evidence regarding patient and community values and preferences is very limited, and generally of low quality. Nevertheless, the conceptual framework that guided the panelists stresses the need to do the best job possible of ensuring that recommendations are consistent with patient and community values. Where panelists perceived values and preferences might vary and were crucial, they explicitly articulated the values underlying particular recommendations.

The ACCP guidelines are important not only for clinicians, but are used by litigating attorneys and by the pharmaceutical industry to promote their antithrombotic drugs. For these reasons, and for reasons of scientific integrity, every effort has been made to remove bias from the recommendations. The panelists who write the chapters and make the recommendations are from diverse institutions. Each chapter is reviewed by at least two editors, and modifications are made through an iterative process. The recommendations are made available and presented to all participants at an open 2-day meeting at which controversial issues are debated extensively. Finally, we have introduced an innovation to further increase the rigor of the guidelines by adding an external review process. Under the oversight of the ACCP Health and Science Policy Committee, the review process has been extended by including nearly 30 individuals from the ACCP Cardiovascular Net-Work, the Health and Science Policy Committee, and the Board of Regents, as well as external peer reviewers at the invitation of the journal.

The ACCP has a policy of constant renewal, replacing panelists and panel chairmen with new members at each iteration. The year 2008 guidelines also herald a change in the Chairmanship of the editors, with the oldest active editor (Jack Hirsh, MD, FCCP) retiring and being replaced for the next iteration by Gordon Guyatt, MD, FCCP. The last 22 years has seen marked improvements in the management of thromboembolic disease, and we can look forward to a bright future with further improvements and innovation.

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DOI: 10.1378/chest.08-0782

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Table 2—Trends in Panel Composition Over Eight Editions

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Resource allocation consultants, No.

Patient values and preferences consultants, No.
Genetics, Iron, and ALI

An Intriguing Relationship

Acute lung injury (ALI), a major cause of morbidity and mortality worldwide, remains a challenge for clinicians and scientists despite decades of investigation. Although substantial progress has been made in understanding the pathogenesis of ALI and, recently, mortality has been decreased by reevaluating the approach to mechanical ventilation in patients with the syndrome, there are still major voids in our knowledge. To date, we are able to predict neither who will acquire ALI nor who will survive, and there are not yet any beneficial pharmacologic interventions. Within the last decade, however, a number of factors have been identified that help to explain the apparent lack of progress and provide opportunities for the development of targeted therapeutic interventions. These include the recognition that the definition of the syndrome, patient variables, and environmental interactions are all critically important in this syndrome. Not only do the incidence and outcome from ALI vary with specific risk factors including sepsis and trauma, and pulmonary vs nonpulmonary factors, but preexisting factors including age, gender, and race, and comorbid conditions such as diabetes and alcohol abuse also impact incidence and outcome.

The tremendous heterogeneity that exists among patients at risk for and with ALI likely explains the apparent lack of benefit from any of the pharmacologic interventions that have been studied. In light of the significant differences in biomarkers in these various patient groups, it makes sense that one therapy is not likely to benefit all; rather, a new approach that allows for the development of targeted therapeutic interventions is more likely to be successful.

The focus on patient heterogeneity has led to an explosion of studies focused on the genetics of patients at risk for and with ALI that have significantly enhanced the understanding of the syndrome. The study by Legan and colleagues is the most recent of these studies and exemplifies both the difficulty in designing and executing these studies and the potential for important contributions from them. The nature of ALI does not lend itself to traditional family-linkage studies. The late onset of the disease, the rapidity with which it develops, and the complexity of the pathogenesis and heterogeneity of the patient population make the candidate gene approach the most utile. Candidate genes are usually chosen from either disease-association studies or studies that suggest biological plausibility. Legan and colleagues chose to study a panel of genes involved in iron metabolism. Oxidative and nitrosative stress are both important in the pathogenesis of ALI/ARDS, and iron is a critical catalyst for numerous reactions that contribute to those stresses. Furthermore, animal studies have demonstrated that iron is important in the pathogenesis of ARDS and clinical studies have shown a relationship between serum ferritin levels and the development of the syndrome. Thus, the choice of the candidate genes was based on sound biological plausibility.

Legan and colleagues chose a case-control study design, a common choice for genetic studies in critically ill patients. The success of case-control studies in these patients depends heavily on the clarity of the diagnosis of the patient population being studied and the choice of the control group. The study by Legan and colleagues highlights both of these complexities. The study population was defined as white patients with ARDS, the more severe form of ALI, and two subgroups were identified: pulmonary or extrapulmonary origin of ARDS. In light of the heterogeneity of patients with ALI/ARDS, the diagnosis of the syndrome must be rigorous and the choice of subgroups can be very important. Unfortunately, the study was retrospective so the determination of the subgroup category and audit of the database to confirm the diagnosis of ALI and other clinical characteristics were dependent on chart review. Furthermore, comorbid conditions including alcohol abuse and smoking that could significantly impact the study results could not be evaluated. The control population consisted of healthy white volunteer blood donors from a single blood transfusion center.

Legan and colleagues found that a ferritin light-chain gene – 3381 GG homozygote was increased in patients with ARDS, particularly the extrapulmonary group, compared to normal control subjects, and a haplotype in heme oxygenase 2 gene was decreased in patients compared to normal subjects. This latter effect was greater in the pulmonary group. Thus, there was a difference in genes that contribute to iron homeostasis between normal control subjects.
and patients with ARDS. This finding is important because it leads further biological evidence to support the hypothesis that iron may be important in ARDS and suggests the need for further studies. However, the data do not confirm that these genetic polymorphisms are associated with the development of ARDS or are specific for ARDS. The polymorphisms could be associated with the risk factors for ARDS or genetic susceptibility to other concomitant processes such as ventilator-associated lung injury could have contributed to the study results, but neither of these possibilities would have been detected by study design chosen. The determination of the importance of genetic regulation of iron metabolism in ALI/ARDS will require substantial additional investigation including case-control studies comparing carefully defined patients with ALI/ARDS and patients at risk for ALI/ARDS as well as studies both in vitro and in animal models. However, the preliminary results from the study of Legan and colleagues suggest that those studies should be considered because they could contribute to the ultimate development of targeted therapeutic interventions for patients with ALI/ARDS, a critically important goal in this devastating syndrome.

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DOI: 10.1378/chest.07-2910

Biomarkers in COPD
Are We There Yet?

COPD is among the top 10 conditions that affect the world population. Its prevalence has risen by 41% since 1982, and its age-adjusted mortality rate increased by >100% between 1970 and 2002. These trends are projected to continue into the foreseeable future. Dissimilar to other major causes of mortality, such as ischemic heart disease, stroke, and HIV/AIDS, there is a dearth of effective interventional strategies that can modify the natural course of COPD. In particular, to our knowledge, there are no known pharmacologic therapies that can reduce the progressive and relentless decline in lung function that characterizes COPD. A major impediment in drug discoveries has been the lack of lung-specific biomarkers that can be used as an intermediate end point for short-term (and less costly) clinical trials. An ideal biomarker is one that (1) has biological plausibility in terms of its role in the pathogenesis of the disease, (2) is associated with a clinically important outcome such as mortality, and (3) can be modified (by an effective intervention) to change the target outcome of interest. In COPD, we have no established biomarkers that fulfill all of these criteria.

One of the major barriers to biomarker discovery in COPD has been the difficulty accessing suitable lung tissue specimens for biomarker identification. In the past, induced sputa, BAL fluid, bronchial biopsy specimens, and exhaled breath condensates have been investigated as potential sources for biomarker discovery. However, major methodological shortcomings, including the invasiveness of the procedures, poor reproducibility, and/or lack of a stan-
standardization of measurements have limited their clinical application. With the growing awareness of COPD as a systemic disease, there has been a shift in the focus of biomarker discovery away from lung sources and toward blood specimens. Serum or plasma biomarkers are attractive because blood is readily available and their measurement can be easily standardized. More recent publications have further fueled the excitement by showing that certain blood-based biomarkers such as C-reactive protein (CRP), interleukin-6, pulmonary activation-regulated chemokine, and inhibitors of plasminogen activators relate to lung function and even to hard clinical outcomes such as exacerbations, morbidity, and mortality. Of these blood-based biomarkers, CRP has shown the greatest promise. There are now at least two major epidemiologic cohort studies that have separately demonstrated that raised blood CRP levels are associated with major outcomes of interest in COPD, including reduced lung function, hospitalization, and mortality, independent of the effects of smoking. CRP levels also relate to poor health status and increased risk of exacerbations.

In this context, the report by de Torres and colleagues in this issue of CHEST (see page 1336) therefore comes as a surprise. The authors carefully studied 218 patients with moderate-to-severe COPD at two different sites and found that baseline CRP levels did not influence the mortality rate in this population. Physiologic measurements such as FEV₁, arterial oxygen tension, inspiratory capacity/total lung capacity ratio, and the distance achieved on a 6-min walk test, on the other hand, were related to mortality, as previously reported. Superficially, these findings appear to contradict the large body of published literature on CRP and COPD, but a closer examination reveals subtleties that may explain the differences.

First, although CRP levels have been associated with mortality in large epidemiologic studies, the relationship was rather weak with large scatter in the data. One study required a sample size of >1,300 participants, while another study required a sample size approaching 5,000 subjects to demonstrate a statistically significant relationship between CRP and health outcomes (e.g., mortality and hospitalization). Second, the present study enrolled patients with moderate-to-severe disease who were symptomatic from their disease in contrast to the previous studies in which asymptomatic or minimally symptomatic subjects were studied. It may be that CRP loses its predictive ability in more severe stages of the disease. Third, in the study by de Torres et al, over half of the patients were receiving inhaled corticosteroids and many had multiple comorbidities; whereas, the subjects in the previous studies were relatively free of drugs and comorbid conditions. Since comorbidities and certain drugs modify CRP levels, these factors may have further weakened the relationship between CRP and mortality.

Notwithstanding these issues, the study by de Torres et al is important for several reasons. First, it suggests that although the CRP levels reported in large studies correlate loosely with morbidity and mortality, they are unlikely to be a good biomarker in COPD because it lacks specificity for COPD outcomes. This may not be surprising given that CRP is synthesized predominantly by hepatocytes (and not by the lungs) and as such is a general (and not a lung-specific) biomarker of systemic inflammation. Moreover, plasma CRP levels are influenced by a host of nonpulmonary factors, including age, sex, drugs, and comorbidities, which limits their clinical application in COPD patients. Second, in patients with moderate-to-severe disease, physiologic parameters such as FEV₁ and inspiratory capacity/total lung capacity ratio are still the most robust and useful methods for stratifying risk in COPD patients. However, as previously stated, these parameters do not necessarily show a response even when interventions known to improve mortality are applied (e.g., supplementary oxygen therapy for hypoxemic COPD patients), making them less than ideal biomarkers. Third, and most importantly, these findings highlight the urgent need to identify novel lung-specific biomarkers that can be used to more accurately stratify the risk of patients and can act as intermediate surrogates for hard outcomes.

COPD is a worldwide epidemic. The identification of robust, reliable, and reproducible plasma biomarkers would be a major boost to the development of new drugs and other interventions to improve the health outcomes of our patients who have this disease. Although we have made major gains in biomarker knowledge over the past decade, as elegantly shown by de Torres and colleagues, we are not there yet! But we need to get there.
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Is Withholding Life Support Associated With a Premature Death?

If So, What Does This Mean for ICU Practice?

The practice of withholding life-sustaining treatments in the ICU typically occurs when the conditions of one or both of two premises are met. The first premise is that the prognosis for survival is poor, even with life-sustaining treatment, and that withholding these treatments will not affect the ultimate outcome. The second premise is that the potential benefits of treatment, in terms of quantity and quality of life, are not, in the judgment of the patient (or of the surrogate decision maker) worth the burden of these treatments.

The article in this issue of CHEST (see page 1312) by Chen et al1 tests the hypothesis that there are no differences in 60-day survival rates between ICU patients for whom life-sustaining treatments were withheld and well-matched patients for whom these treatments were not withheld. In formulating this hypothesis, the authors assumed that the first premise was the predominant rationale for withholding life-sustaining treatments in the ICU. The authors rejected their hypothesis after finding a twofold increase in the risk of death at 60 days for those patients who had life-sustaining treatment withheld. They based their analysis on observational data, which leaves one to wonder whether there are issues of bias that may account for the difference between the groups; in other words, are there unmeasured variables that might account for the decreased survival rate among those patients who have life-sustaining treatments withheld? If the answer to this question is “no,” the next question to answer is what does this tell us about our current practice of withholding life support?

The authors’ ability to reject their hypothesis rests on their use of a propensity score, a technique used to match patients on measurable characteristics. Propensity scores are a powerful tool to adjust for bias in observational studies. The samples generated using propensity score matching would be functionally equivalent to randomized samples if the variables included in the model accounted for all factors that matter in predicting who received the treatment, or, in this case, who has life-sustaining treatments withheld. However, propensity-scoring methods are limited by what can be measured; often, key variables of interest are not readily available or are difficult constructs to measure accurately (eg, severity of illness).

There are many important variables that could be associated with a decision to withhold life-sustaining treatments in the ICU and therefore might be useful to include in a propensity score. Chen and colleagues’ propensity score model includes 69 variables, representing patient demographics, severity of illness, comorbidities, ICU admitting diagnoses, and ICU admission source. Yet, as acknowledged by the authors, there were also a number of unmeasured variables that could not be included, such as the patient’s initial response to treatment, the baseline quality-of-life assessments, religiosity, concerns about being a burden, and patient and family preferences for life-sustaining treatments. Another unmeasured
variable that deserves attention is the clinicians’ estimate of prognosis for survival, which tends to be a better predictor at the extremes of prognosis than objective scores such as the APACHE (acute physiology and chronic health evaluation) II score. Furthermore, clinicians’ estimates of prognosis, regardless of their accuracy, have an important effect on decisions to withhold life-sustaining treatments. In the study by Chen et al., the lack of clinician assessments in the equations could account for the difference in survival rates between the groups.

After controlling for the patient factors they had available to them, Chen and colleagues found that patients who had life-sustaining treatments withheld had a twofold increased risk of death at 30 and 60 days. However, it is also noteworthy that in the Cox regression survival analyses, the differences in mortality between those who did and did not have life-sustaining treatments withheld decreased over time, with a hazard ratio that dropped to 1.05 at 1 year. These findings suggest that, while the differences in mortality rates may be sustained for up to 1 year, the relationship seems to diminish over time.

Overall, these findings focus attention on what might be considered “premature deaths” in the ICU because of decisions to withhold life-sustaining treatments. If we concur with the authors that the propensity score method sufficiently accounts for potential confounders that could contribute to differences in mortality rates, the next question is how do we evaluate the appropriateness of these premature deaths? We could define appropriate premature deaths as deaths in which patients, families, and clinicians would agree that the expected burden of treatment outweighed the expected benefits for survival, or that the expected quality of life after critical care reflected what would be considered by the patient as a “health state worse than death.” This is the second premise we described above. On the other hand, inappropriate premature deaths would be those in which prognostication errors negatively affect the ability to make informed assessments of treatment burdens and potential outcomes, and in which patients and family members would have chosen to continue life-sustaining treatment had the prognostication for quantity and quality of life been more accurate. The study by Chen and colleagues cannot differentiate these “appropriate” and “inappropriate” premature deaths, but their article encourages future researchers to find ways to explore these issues.

We believe that the article by Chen and colleagues, although not definitive, suggests evidence of premature death at 60 days among patients for whom treatments are withheld, and that these patients may continue to have higher mortality rates (although diminishing over time) up to 1 year. Future studies are needed to confirm these findings as well as to examine some of the important unmeasured variables. This article cannot tell us to what extent such premature deaths might represent a problem, and we do not believe the results of this article should be interpreted as an indictment of current clinical practice. However, the article highlights the importance of assuring that decision making about withholding life-sustaining treatments involves a careful assessment of prognosis and thorough communication with patients and their families. The fact that many physicians experience pressure to withhold life-sustaining treatments and that ICU clinicians place a lower value on life-sustaining treatments than patients and family members should give us pause and encourage us to look critically at our own practices. The authors note that “there are no formal protocols mandating the timing, frequency, or content of discussions with patients and families about life support options” at their institution. Introducing systematic approaches to ensure that these discussions happen is key to improving care in the ICU. A necessary step includes improving discussions of patients’ values and preferences, and of the goals of care, as well as routinely documenting these discussions in the medical record. In the context of high-quality communication about values, preferences, and goals, the appropriate use of life-sustaining treatments would be measured not by the intensity of therapy or even the duration of survival, but rather by the degree to which the goals of care matched the goals of informed patients and their families. Such an approach would inherently recognize the importance of palliative care in the ICU and would acknowledge that death is not always an adverse outcome.

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