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

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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]



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 1986,¹ 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.² Over the past 2 decades, these guidelines have adapted to trends in evidence-based medicine and helped to raise the standards for guideline methodology.^{3–8} 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 glycopro-

tein 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

Table 1—Trends in Number of Recommendations and Quality of Evidence Over Eight Editions of the Guidelines*

Variables	1986	1989	1992	1995	1998	2001	2004	2008
Recommendations, total No.	73	129	142	201	217	260	562	741
A1 or 1A recommendations, No.	16	31	31	34	49	50	123	182
Proportion of 1A recommendations, %	22	24	22	17	23	19	22	25

*The 1A recommendations were referred to as “A1” recommendations in earlier publications of the guidelines.

Table 2—Trends in Panel Composition Over Eight Editions

Variables	1986	1989	1992	1995	1998	2001	2004	2008
Panelists, No.	32	40	52	70	80	85	91	102
United States	25	29	35	48	54	52	51	46
Canada	5	7	14	15	18	22	21	20
Europe	2	4	3	7	8	9	18	21
Other	0	0	0	0	0	2 (Mexico and Australia)	1 (Australia)	1 (Australia)
Resource allocation consultants, No.								2
Patient values and preferences consultants, No.								3

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 anti-thrombotic 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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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,¹ 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.^{2–4} 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,⁵ 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 en-

hanced the understanding of the syndrome.^{6–8} The study by Legan and colleagues⁹ 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 colleagues⁹ 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.^{9,10} Thus, the choice of the candidate genes was based on sound biological plausibility.

Legan and colleagues⁹ 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 colleagues⁹ 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 results¹¹ could not be evaluated. The control population consisted of healthy white volunteer blood donors from a single blood transfusion center.

Legan and colleagues⁹ 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

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