Commentary in Response to Controversies in Nephrology

Anemia of Kidney Disease and Clinical Practice Guidelines: Quo Vadis?

Jonathan Himmelfarb,* William Henrich,† and Thomas DuBose‡

*Maine Nephrology Associates, Portland, Maine; †University of Texas Health Science Center at San Antonio, San Antonio, Texas; and ‡Wake Forest University School of Medicine, Winston-Salem, North Carolina

I n the 15 yr since the Institute of Medicine defined clinical practice guidelines (CPG) as “systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances” (1), there has been an upsurge in their promulgation. The Agency for Healthcare Research and Quality lists more than 2000 active CPG. The factors that have driven the profusion of clinical practice guidelines are essentially the same that have driven a general increase in evidence-based decision-making and the field of outcomes research. Evidence strongly suggests that standardization of medical practice can provide cost-effective care that improves outcomes (2).

Despite the seemingly compelling virtue of CPG, they are certainly not a panacea for all of the ills in health care delivery. CPG usually focus on improving the management of one particular disease, often neglecting to provide guidance on the integration of complex medical regimens for patients with multiple comorbid diseases (3,4). When CPG are linked to clinical performance measures, the result can be an increase in auditing and regulation without necessarily improving patient outcomes (5,6). Grading evidence for CPG remains complex, with multiple varying systems and approaches available (7,8). Different conclusions can arise when applying different grading systems to the same body of evidence (9). Furthermore, the use of the same methodologic approach by different users may result in different evidence grades (10). Therefore, judgment, value, and opinion on the part of graders are critical for the final work product despite the use of objective, structured approaches. Of importance, CPG development rarely takes costs into consideration; indeed, it has been recommended that guideline panels focus primarily on determination of net medical benefits with a viewpoint that costs can be considered separately (11). This is not withstanding the important downstream economic impact if clinicians adhere to CPG.

The discipline of nephrology has expended immense effort toward CPG development. Few who have been directly involved in the care of patients with CKD and ESRD in the past decade would dispute the cumulative net value that these guidelines have had in improving the quality of care that is delivered to patients with kidney disease. In particular, the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines have had perhaps the widest impact on standardizing and improving clinical care for patients with kidney disease. The KDOQI guidelines, taken together, have benefited numerous patients by raising standards and by improving quality through more careful surveillance of patients with kidney disease. Selected KDOQI CPG have also been translated into Clinical Performance Measures by the Centers for Medicare and Medicaid Services, thereby further augmenting their clinical impact. Nonetheless, in the Controversies in Nephrology section in the January issue of CJASN, Coyne (12) raised important questions regarding transparency and conflict of interest in the KDOQI CPG development process. In response, Van Wyck et al. (13) vigorously defended the integrity of the KDOQI process.

The debate and controversy in the January issue bring two important issues into sharp focus: (1) The need for continual research to upgrade the strength of evidence that is used in the development of CPG and (2) the need for vigorous debate and discussion on the clinical science of kidney disease. At best, CPG can only be as first-rate as allowed by the evidence. Historically, nephrology has been seriously underrepresented in use of randomized clinical trials despite being the optimal study design to answer intervention questions. Using a Cochrane Systematic Review approach, Strippoli et al. (14) noted that the number of randomized clinical trials in nephrology that were published from 1966 to 2002 is fewer than all other specialties of internal medicine, with the proportion of all citations that are randomized clinical trials being the third lowest. In a similar vein, Coca et al. (15) and Charytan and Kuntz (16) each recently demonstrated that patients with CKD are underrepresented in randomized, controlled trials of cardiovascular disease.

Much of the current controversy regarding appropriate CPG for anemia management has been stimulated by the recent publication of large, randomized clinical trials that evaluated the outcomes of nondialysis patients who had CKD and were randomly assigned to different target hemoglobins with the use of erythropoietin-stimulating agents (17,18). Recent publications from other large, randomized clinical trials in the dialysis population have also generated considerable debate and discussion in nephrology (19,20), and many other large clinical trials in the advanced CKD and ESRD population are in progress. It is encouraging to note this recent trend toward a reversal of the previous paucity of large, well-conducted, randomized trials. Supplementary evidence can only strengthen future iterations of CPG and result in improved care for patients with kidney disease. Because most CPG have a built-in method for reconsidering and revising guidelines as new evidence becomes available, it is anticipated that clinical guidelines will undergo evolutionary change. Ac-
cordingly, the anemia guidelines group of KDOQI has elected to reconsider their recommendations in light of the recent Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR)/Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin β (CREATE) data.

As a professional society, the American Society of Nephrology (ASN) is dedicated to providing a forum for the promulgation of new knowledge through research and to enhance and assist the study and practice of nephrology. As evidenced by the recent creation of a Public Policy Board, the ASN is also dedicated to assisting (on a policy level) in the translational step of bringing the best possible medical care to patients with kidney disease. Through its journals and numerous educational programs, the society remains dedicated to vigorous debate and responsible discussion on many controversial issues. As of now, there are no plans for the ASN to develop guidelines for practice. Rather, the society sees its role as providing the forum where the latest science in clinical and basic domains can be evaluated and debated. In this regard, during the recently completed 39th Annual Meeting of the ASN, there were many presentations of the latest information on the treatment of the anemia of kidney disease. This is in conformity with our belief that rigorous clinical science, open communication, vigorous debate, and proper oversight that are designed to minimize conflicts of interest are the best means to improve care for patients with kidney disease.

Disclosures
None.

References

Clearly, anemia guidelines continue to be somewhat controversial, including determining the exact target for hemoglobin with erythropoietin therapy as well as the role of parenteral iron in patient management. In this month’s issue of JASN, a study by Coyne et al. (pages 975–984) randomizing patients to no iron versus IV iron gives some insights into the efficacy of parenteral iron in patients receiving adequate erythropoietin dosage. Clearly, abnormalities in iron metabolism must be factored into a multidisciplinary approach to patient management.