Through the Looking Glass: Anemia Guidelines, Vested Interests, and Distortions

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The most recent National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease, released in May 2006, has led to intense debate and scrutiny in both the scientific and the lay press. At issue are the process and the timing of the report, the role of participants and of industry, and the quality of the data used in making recommendations. Suggestions in both the press and medical journals that vested interests might have resulted in recommendations that might be unwarranted and harmful have reflected adversely on the guidelines, irrespective of the good intentions of those who wrote them. In light of this media maelstrom, it is worthwhile to consider the history of both guidelines and the problem of anemia in chronic kidney disease (CKD). It has been nearly two decades since Eschbach et al. (1) reported the results of phase 1–2 study in 25 patients and then a phase 3 study (2) that demonstrated that erythropoietin could correct anemia in patients who receive dialysis, averting the need for transfusion and its attendant risks. Since those first clinical studies about erythropoietin, the course of severe anemia in CKD, as well as its attendant risks, has been greatly altered in a generally positive direction.

In recent years, the question has focused not on whether to use agents that stimulate erythropoiesis, but how best to use such agents in our patients. The data necessary to inform the optimal correction of anemia have not been definitive, and new trials were designed to address the issue. Concomitantly, guidelines that were based on available data, revised over time, have played a prominent role in shaping our medical decisions about anemia and other aspects of renal disease. The most recent version of the KDOQI anemia guidelines was a complex and nuanced document that contained many recommendations, among which was an increase in the recommended level for correction of anemia (3). At the time the latest guidelines were released, a number of controlled trials were in still progress. Among these, two studies in patients who had CKD and were not yet on dialysis, Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin β (CREATE) and Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR), published in November 2006 (4,5), added weight to existing concerns that complete correction of anemia might be associated with increased cardiovascular risk. Shortly thereafter, a hearing of the US House Ways and Means Committee and a Government Accountability Office study on payment for ESRD services received much attention in the press (6). In addition, evidence of erythrocyte-stimulating agent toxicity among cancer patients (7) plus an Food and Drug Administration warning in November, followed by an update with Black Box warning in March 2007, have fueled these debates (8). Although further studies are ongoing, it has been suggested by some that “the answer is in” on correction of anemia (9), whereas others argue for continuing studies (10). A recently published meta-analysis (11) that combined studies in both dialysis patients and patients with CKD suggested increased cardiovascular risk, although there were substantial differences in many of the trials that were included in the study.

A vibrant airing of the complex issues around guidelines and anemia has appeared in the pages of CJASN in the past few months (12–23). The issues raised placed authors in several camps with widely differing views. All of the commentaries that CJASN has published—as well as those published elsewhere (9,24)—have, at their core, the commitment to provide optimal care for patients. These commentaries consider the ethical aspects of clinical practice guidelines, the level of influence from Pharma on the guideline process, and the sufficiency of the data. Criticism of the KDOQI process itself and the funding of the anemia guidelines in particular, as well as the participation of experts with ties to industry, varied from highly critical (13,15) to zero tolerance (22). The suggestion that most experts worth their salt would have commercial funding has been called reasonable by some and arrogant by others, as has the argument that those who are not conflicted would be insufficiently knowledgeable. Other commentators noted that we all have conflicts of interest that are harder to pinpoint than financial, for example, intellectual and emotional conflicts of interest (18). Going beyond this, Amerling and Winchester (19) suggested that guidelines are worthless and can do more harm than good, pointing out that physicians need to make individualized treatment decisions.

As this series of commentaries in CJASN has demonstrated (12–23), there is huge interest in guidelines in our community, and we all have a stake in these guidelines—be we nephrologists, referring doctors, or patients. As nephrologists, guide-
lines for treating kidney disease and its attendant complications inevitably will change how we view certain conditions and how we will treat them. As practitioners, we hope that guidelines will lead to optimal health for our patients and nothing less.

The development of guidelines involves a participatory process that requires a huge amount of work to evaluate a vast array of data of widely variable quality. It is important to emphasize that those who agree to take on such work do so seriously and want to do good, not harm. Given the huge amount of labor that is necessitated by the participants in the guideline process and the complexity of the recommendations in the 2006 KDOQI anemia guidelines (3), the criticisms may seem unfair and reductionistic to some. Among the commentators in CJASN, Van Wyck et al. (14,16) and other participants in the KDOQI guidelines outlined the concepts and needs that drove the founding principles for the entire NKF-KDOQI process, which have provided, over time, many important guidelines for the nephrology community. These achievements should not be overlooked. Van Wyck et al. effectively pointed out that their report is multifaceted and nuanced and also have announced that they will reexamine the data about erythropoietin-stimulating agents in light of the CHOIR and CREATE studies. However, Van Wyck et al. do not directly discuss the issue that has been a virtual lightning rod for criticism that has come their way: funding of guideline development, disclosures of industrial affiliations, and conflicts of interest. Further, that the guidelines were released before the publication of the primary data from the CHOIR and CREATE studies has unleashed even further criticism.

A major issue confronting nephrology today is how we can best develop guidelines that provide our patients—and ourselves as clinicians—with treatment recommendations that are free from commercial bias. Financial associations with the manufacturers of medications that we prescribe clearly may influence our clinical judgment and can be pernicious when we create guidelines; yet it is obvious, in an era when it seems that a majority of clinical trials have industry funding (25), that many clinical investigators will have at least some associations. At least some leading experts in each field will have done research or will have consulted for entities that produce the very medications and devices that they study. Therefore, beyond the membership of guideline panels, the research on which we base guidelines is potentially influenced by entities that may have financial interests in the outcome.

In addition, in an era when funding for educational and research purposes is difficult to secure, many organizations receive funding from Pharma and Biotech (24,25). As nephrologists, we cannot help but be aware that ASN, NKF, Renal Physicians Association, American Society of Transplantation, American Society of Pediatric Nephrology, and International Society of Nephrology (to name some of our organizations) all receive industry funding. Much if not most of that funding is used directly or indirectly to support patient care, to underwrite educational meetings, and to support a variety of projects. This situation is not unique to our specialty but is true for virtually all medical specialties. If we participate in our organizations but do not ourselves have funding, then are we free of commercial influences? We all should look in the mirror before castigating colleagues.

This being said, where, as a community, should we go from here? If pharmaceutical firms directly fund guidelines for diseases that are treated with their medications, then how can there not be an inherent conflict of interest? Optimally, we need and want guidelines to provide our patients with the safest and most effective care possible. We and they deserve recommendations that are based on the very best evidence available—recommendations that we can use to inform the choices that we face with each individual patient. To create useful and credible guidelines, we need to scrutinize the available data in as unbiased a manner as possible, yet what we believe to be true today may change with more information, irrespective of the funding source. Furthermore, as was evident in the many viewpoints about the anemia guidelines expressed within the pages of CJASN, the manner in which guidelines are developed and disseminated deserves careful reexamination. A major lesson from the debate about the anemia guidelines is that we must revisit the guideline process to ensure transparency and clarity. We want the most experienced and critical panelists and organizations to review and assess the data and make recommendations. It seems unrealistic to mandate that the government should sponsor all guidelines. Zero tolerance for commercial relationships may be the ideal for selecting panelists, but it may not be straightforward to accomplish. A de minimus and complete disclosure would be more feasible. Furthermore, at the end of the day, it is obvious that links or the appearance of links between pharmaceutical sponsors and clinical practice guidelines diminishes the value of guidelines.

Disclosures

Dr. Ingelfinger has no financial disclosures. She is a deputy editor at the New England Journal of Medicine. She is also a past president of the local NKF Affiliate of MA, RI, NH, and VT, a purely voluntary position.

References


