The Current Status of Anemia Management: KDIGO Guidelines

By Rebecca J. Schmidt

The introduction of erythropoietin-stimulating agents (ESAs) in the late 1980s revolutionized the treatment of anemia for patients with chronic kidney disease (CKD), with the ensuing parade of clinical trials serving as the scientific basis for current management principles. Unlike other fields, CKD-related anemia management has been challenged by a windstorm of regulatory events and payment policies affecting the particulars of managing this important complication of CKD. The principles of management today reflect this regulatory influence on scientific discovery and collective clinical experience.

Current guidance

A comprehensive evidence-based guideline for managing CKD-related anemia, the Kidney Disease: Improving Global Outcomes (KDIGO) guideline, was developed by an international team of experts together with an evidence review team using the Grading of Recommendations, Assessments, Development, and Evaluation (GRADE) template for guideline recommendations by strength of recommendation (A–D) (1). Most of the recommendations are not graded but are presented as a consensus of expert opinion and serve as guidance for today's standard of practice. Most of the nongraded recommendations are noncontroversial and represent what might be characterized as common sense. The few recommendations graded as 1 (strong) or based on evidence of highest quality (A) relate to cautionary concerns such as targeting the hemoglobin (Hb) to a level below 15 g/dL and the administration of dextran-based intravenous iron. The quality of evidence throughout is not consistently strong, leaving significant room for clinical judgment (Figure 1).

A different form of guidance became dominant, with changes in reimbursement and regulatory policies beginning in 2011. The substantial reduction in ESA use and Hb levels occurring subsequently in the United States (2), along with concurrent increases in use of iron supplementation and blood transfusions between 2006 and 2015 (3,4), has been seen as a response to reimbursement policy and regulatory directives.

Status quo versus quagmire state

Although much has changed for the nephrologist managing CKD-related anemia in the past 20 years, basic tenets remain. The evolution of protocols and the institutionalization of anemia management might seem to imply that less interpretation is needed; however, the wide scope of evidence strength acknowledged in the guideline suggests otherwise and underscores the primacy of clinical decision-making. A targeted clinical assessment with special attention to iron stores and the propensity of occult gastrointestinal bleeding in CKD patients remains the basis for evaluation of CKD-related anemia. Potentially correctable causes of anemia that might be operative in addition to erythropoietin deficiency constitute a priority of investigation. There continues to be no recognized role for erythropoietin levels.

Health-related quality of life benefits are not considered an indication for use by the U.S. Food and Drug Administration; therefore, the level of 11 g/dL is the upper limit of cut-off. Despite the acknowledgment by KDIGO that some patients may benefit from a higher Hb, widespread concern for reimbursement discourages efforts to supersede this level. The recommendation to decrease rather than hold ESAs in the event of a rising Hb remains, and protocols are designed to account for this.

Blood transfusions are appropriate for emergent anemia treatment; their avoidance is included as a criterion for warranting the use of ESAs. Finally, the rationale for the use of intravenous iron over oral preparations remains a matter of risk versus benefit. KDIGO generally recommends the intravenous over the oral route in adult CKD patients, although that recommendation is less than strong, requiring the individualization of a treatment plan balanced for benefit and risk.

Strides forward versus entropic movement

Greater use of longer-acting ESAs has provided additional clinical experience: remarkably similar Hb levels have been achieved by a variety of short-acting and long-acting agents (5). In the spirit of entrepreneurship, biosimilar agents for stimulating erythropoiesis are on the horizon, promising more options for patients and physicians—this, of course, tempered by financial, practical, and institutional constraints. New oral agents for iron appear to be more effective than those traditionally purchased over the counter (6), and with their ability to act as binders, there is opportunity for reducing a patient's daily medication intake.

Figure 1. Current status of anemia management

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add to the lingering concerns and questions surrounding the iron aspects of anemia management.

Finally, greater scrutiny of costs of the ESRD program has prompted attention to the costly transition from CKD 4–5 to 5D, when incident patients without prior CKD care abruptly start dialysis. Patients treated with ESAs before and after hemodialysis initiation who maintained a Hb of 9.0 g/dL had a lower risk of all-cause mortality at 3, 6, and 12 months than did patients with a Hb of less than 9 g/dL before hemodialysis initiation (with or without ESA) whose levels increased with ESAs after hemodialysis initiation (12). Findings of this nature, in addition to reports that healthcare resource utilization is higher in anemic patients than in nonanemic patients (3), pave the way for future research in this arena.

Primacy of clinical judgment and “first do no harm”

Clinical judgment is championed in the KDIGO guideline, underscoring the importance of physician involvement and oversight in clinical decision-making for any given patient. Evolving clinical experience coupled with fine-tuning of protocols has culminated in a management standard that integrates nurse-driven algorithm-directed treatment decisions with physician oversight. As scientific discovery continues to drive guideline development, and regulatory influences intertwine with clinical experience to affect protocols, there remains wisdom in clinical judgment and the simplicity of common sense.

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References