The Official Journal of the National Kidney Foundation

AJKD American Journal of Kidney Diseases

VOL 47, NO 5, SUPPL 3, MAY 2006

# CONTENTS

# KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease

# KDOQI Disclaimer

*SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINES AND CLINICAL PRACTICE RECOMMENDATIONS*

These Clinical Practice Guidelines (CPGs) and Clinical Practice Recommendations (CPRs) are based upon the best information available at the time of publication. They are designed to provide information and assist decision-making. They are not intended to define a standard of care, and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every health-care professional making use of these CPGs and CPRs is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation. The recommendations for research contained within this document are general and do not imply a specific protocol.

*SECTION II: DEVELOPMENT PROCESS*

The National Kidney Foundation makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional or business interest of a member of the Work Group.

Specifically, all members of the Work Group are required to complete, submit and sign a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest. All affiliations are published in their entirety at the end of this publication in the Biographical Sketch section of the Work Group members.

In citing this document, the following format should be used: National Kidney Foundation. *KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease.* Am J Kidney Dis 47:S1-S146, 2006 (suppl 3).

Support for the development of the KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease was provided by Amgen, Inc.

AMGEN®

The National Kidney Foundation gratefully acknowledges the support of Amgen, Inc. as the founding and principal sponsor of KDOQI.

# Tables

## Figures

# Acronyms and Abbreviations

| | |
|---|---|
| $\Delta$ | Change |
| $\uparrow$ | Increase |
| $\downarrow$ | Decrease |
| ABP | Ambulatory blood pressure |
| ABPM | Ambulatory blood pressure monitoring |
| ACE | Angiotensin-converting enzyme |
| ADE | Adverse drug event |
| AE | Adverse event |
| ARBs | Angiotensin receptor blockers |
| ARF | Acute renal failure |
| AST | Aspartate transaminase |
| BID | Twice daily |
| BIW | Twice weekly |
| BP | Blood pressure |
| BSA | Body surface area |
| CABG | Coronary artery bypass graft |
| CBC | Complete blood count |
| $C_{Cr}$ | Creatinine clearance |
| CESDS | Center for Epidemiologic Studies Depression Scale |
| CFU-E | Erythroid colony-forming units |
| CHF | Congestive heart failure |
| CHOIR | Correction of Hemoglobin and Outcomes in Renal Insufficiency |
| CHr | Content of hemoglobin in reticulocytes |
| CI | Confidence interval |
| CKD | Chronic kidney disease |
| CMV | Cytomegalovirus |
| CPG | Clinical practice guideline |
| CPR | Clinical practice recommendation |
| CREATE | Cardiovascular Risk Reduction by Early Anemia Treatment With Epoetin Beta Trial |
| CRI | Corrected reticulocyte index |
| CV | Cardiovascular |
| CVA | Cerebrovascular accident |
| CVD | Cardiovascular disease |
| D/C | Discontinuation |
| DBP | Diastolic blood pressure |
| DNA | Deoxyribonucleic acid |
| DOQI | Dialysis Outcomes Quality Initiative |
| EBPG | European Best Practices Guideline |
| eGFR | Estimated glomerular filtration rate |
| ERI | Erythropoietin resistance index |
| ERT | Evidence Review Team |
| ESA | Erythropoiesis-stimulating agent |
| ESRD | End-stage renal disease |
| FACIT | Functional Assessment of Chronic Illness Therapy |
| FDA | Food and Drug Administration |
| GFR | Glomerular filtration rate |
| GI | Gastrointestinal |
| Hb | Hemoglobin |
| Hct | Hematocrit |
| HD | Hemodialysis |

| | |
|---|---|
| HD-CKD | Hemodialysis-dependent chronic kidney disease |
| HDF | Hemodiafiltration |
| HPS | Hemophagocytic syndrome |
| HTN | Hypertension |
| HU | Hydroxyurea |
| HUI | Health Utilities Index |
| HUS | Hemolytic uremic syndrome |
| IHD | Ischemic heart disease |
| IM | Intramuscular |
| IU | International Unit |
| IV | Intravenous |
| KDIGO | Kidney Disease: Improving Global Outcomes |
| KDOQI | Kidney Disease Outcomes Quality Initiative |
| KDQ | Kidney Disease Questionnaire |
| KDQOL | Kidney Disease Quality of Life |
| KEEP | Kidney Early Evaluation Program |
| KLS | Kidney Learning System |
| KPS | Karnofsky Performance Scale |
| LV | Left ventricular |
| LVD | Left ventricular dilation |
| LVEDd | Left ventricular end-diastolic diameter |
| LVH | Left ventricular hypertrophy |
| LVMI | Left ventricular mass index |
| LVVI | Left ventricular volume index |
| MAP | Mean arterial blood pressure |
| MCH | Mean corpuscular hemoglobin |
| MCHC | Mean corpuscular hemoglobin concentration |
| MCV | Mean corpuscular volume |
| MDRD4 | Modification of Diet in Renal Disease |
| MI | Myocardial infarction |
| MR | Mitral regurgitation |
| N, n | Number of subjects |
| N/A | Not applicable |
| NAPRTCS | North American Pediatric Renal Transplant Cooperative Study |
| nd | Not documented |
| ND-CKD | Non–dialysis-dependent chronic kidney disease |
| NHANES | National Health and Nutrition and Examination Survey |
| NKF | National Kidney Foundation |
| NOS | Not otherwise specified |
| NS | Not significant |
| OR | Odds ratio |
| PD | Peritoneal dialysis |
| PD-CKD | Peritoneal dialysis–dependent chronic kidney disease |
| PHRBC | Percent hypochromic red blood cells |
| PHRC | Percent hypochromic red cells |
| PO | Oral |
| PRCA | Pure red cell aplasia |
| Pt | Patient |
| PTA | Posttransplantation anemia |
| QoAL | Quality of American Life |
| QOL | Quality of life |

| | |
|---|---|
| QOW | Every other week |
| RCT | Randomized controlled trial |
| rHuEPO | Recombinant human erythropoietin |
| RQoLP | Renal Quality of Life Profile |
| RR | Relative risk |
| SAE | Severe adverse event |
| SBP | Systolic blood pressure |
| SC | Subcutaneous |
| SCD | Sudden cardiac death |
| $S_{Cr}$ | Serum creatinine |
| SF-36 | 36-Item Medical Outcomes Study Short-Form Health Survey |
| SIP | Sickness Impact Profile |
| SQUID | Superconducting quantum interference device |
| TDS | Total daily supplement |
| TID | Thrice daily |
| TIW | Thrice weekly |
| TRESAM | Transplant European Survey on Anemia Management |
| TSAT | Transferrin saturation |
| TTO | Time trade-off |
| TTP | Thrombotic thrombocytopenic purpura |
| Tx-ND-CKD | Non–dialysis-dependent kidney transplant recipient population |
| U | Unit |
| URR | Urea reduction ratio |
| USFDA | United States Food and Drug Administration |
| USRDS | United States Renal Data System |
| vs | Versus |
| WHO | World Health Organization |
| ZPP | Zinc protoporphyrin |

# Anemia in Chronic Kidney Disease

# Work Group Membership

**Work Group Co-Chairs**

David B. Van Wyck, MD
University of Arizona College of Medicine
Tucson, AZ

Kai-Uwe Eckardt, MD
University of Erlangen-Nuremberg
Erlangen, Germany

**Work Group**

John W. Adamson, MD
Blood Center of SE Wisconsin
Blood Research Institute
Milwaukee, WI

George R. Bailie, MSc, PharmD, PhD
Albany College of Pharmacy
Albany, NY

Jeffrey S. Berns, MD
University of Pennsylvania School of Medicine
Philadelphia, PA

Steven Fishbane, MD
Winthrop University Hospital
Mineola, NY

Robert N. Foley, MD
Nephrology Analytical Services
Minneapolis, MN

Sana Ghaddar, RD, PhD
American University of Beirut
Faculty of Agriculture and Food Sciences
Beirut, Lebanon

John S. Gill, MD, MS
University Of British Columbia
St. Paul's Hospital
Vancouver, Canada

Kathy Jabs, MD
Vanderbilt University Medical Center
Nashville, TN

Patricia Bargo McCarley, RN, MSN, NP
Diablo Nephrology Medical Group
Walnut Creek, CA

Hans H. Messner, MD
University Health Network
Princess Margaret Hospital
Toronto, Canada

Allen R. Nissenson, MD
UCLA Medical Center
Los Angeles, CA

Gregorio T. Obrador, MD
Universidad Panamericana School of Medicine
Mexico City, Mexico

John C. Stivelman, MD
Northwest Kidney Center
Seattle, WA

Colin T. White, MD
British Columbia Children's Hospital
Vancouver, Canada

**Liaison Member**

Francesco Locatelli, MD
Azienda Ospedaliera DI Lecco
Lecco, Italy

Iain C. Macdougall, MD
King's College Hospital
London, England

**Evidence Review Team**

National Kidney Foundation Center for Guideline Development and Implementation at Tufts-New England Medical Center, Boston, MA

Katrin Uhlig, MD, MS, Project Director and Program Director, Nephrology
Christina Kwack Yuhan, MD, Assistant Project Director

Amy Earley, BS
Rebecca Persson, BA
Gowri Raman, MD

Ashish Mahajan, MD, MPH
Priscilla Chew, MPH

In addition, support and supervision was provided by:

Joseph Lau, MD, Program Director, Evidence Based Medicine
Ethan Balk, MD, MPH, Evidence Review Team Co-Director
Andrew S. Levey, MD, Center Director

# KDOQI Advisory Board Members

Adeera Levin, MD, FACP
*KDOQI Chair*
Michael Rocco, MD, MSCE
*KDOQI Vice-Chair*

Garabed Eknoyan, MD
*KDOQI Co-Chair Emeritus*

Nathan Levin, MD, FACP
*KDOQI Co-Chair Emeritus*

George Bailie, PharmD, PhD
Bryan Becker, MD
Peter G. Blake, MD, FRCPC, MBB.Ch
Allan Collins, MD, FACP
Peter W. Crooks, MD
William E. Haley, MD
Alan R. Hull, MD
Lawrence Hunsicker, MD
Bertrand L. Jaber, MD
Cynda Ann Johnson, MD, MBA
George A. Kaysen, MD, PhD
Karren King, MSW, ACSW, LCSW
Michael Klag, MD, MPH
Craig B. Langman, MD
Derrick Latos, MD
Donna Mapes, DNSc, MS
Linda McCann, RD, LD, CSR
Ravindra L. Mehta, MD, FACP
Maureen Michael, BSN, MBA
William Mitch, MD
Joseph V. Nally, MD
Gregorio Obrador, MD, MPH
Rulan S. Parekh, MD, MS
Thakor G. Patel, MD, MACP
Brian J.G. Pereira, MD, DM
Neil R. Powe, MD
Claudio Ronco, MD
Anton C. Schoolwerth, MD
Raymond Vanholder, MD, PhD
Nanette Kass Wenger, MD
David Wheeler, MD, MRCP
Winfred W. Williams, Jr., MD
Shuin-Lin Yang, MD

**Ex-Officio**
Josephine Briggs, MD
David Warnock, MD

# NKF-KDOQI Guideline Development Staff

Donna Fingerhut
Margaret Fiorarancio
Richard Milburn
Anthony Gucciardo
Kerry Willis, PhD

The Official Journal of the National Kidney Foundation

VOL 47, NO 5, SUPPL 3, MAY 2006

AJKD American Journal of Kidney Diseases

# Foreword

This publication of the Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia represents the second update of these guidelines since the first guideline on this topic was published in 1997. The first set of guidelines established the importance of hemoglobin in dialysis patients, and established guidelines and targets for the treatment of anemia in dialysis patients. The first update, published in 2000, described anemia in a wider spectrum of the chronic kidney patients, and included those not on dialysis.

A number of important randomized clinical trials and large observational studies have been commenced or completed in CKD populations both on and off dialysis, over the past 5 years. The key questions that have been addressed in these recent studies have been the optimal hemoglobin target for CKD patients. To date there has been little support normalizing hemoglobin, though a number of important studies have not been completed or reported (CHOIR and TREAT), and the community eagerly awaits them. Nonetheless, the key aspects of the published data from both controlled trials and observational studies, support the ongoing importance of hemoglobin levels in risk stratification of patients with CKD, whether with native or transplant kidneys, or on dialysis therapies. Much has been learned about the causes of erythropoietin resistance, and some small studies have reported methods of treating ESA resistance. Furthermore, there are multiple new insights into the optimizing treatment of anemia with iron supplementation and ESA. Novel actions of ESAs on cognitive function, as well as preservation of kidney and cardiac function have been described. To date there are no clinical trials to support the use of ESA for these 'non anemia' purposes, but both the basic and clinical science of ESA therapy are advancing at a rapid pace.

This updated set of guidelines on anemia is unique and different from the previous anemia guidelines. Firstly, the guidelines have been separated into evidence based guidelines and clinical practice recommendations, based on the strength of evidence. The term guideline is reserved for that which is robust enough to be used, if appropriate, as a clinical performance measure. Clinical practice recommendations are those recommendations based on expert opinion of the working group, but lacking sufficient hard data; CPRs are also susceptible to testing in a clinical trial. Secondly, these guidelines incorporated individuals from countries outside the US (Europe, UK, Middle East, Mexico and Canada) and attempted to build on most recently published European Best Practice guidelines (2004), as well as the previously published KDOQI versions. Lastly, the working group was clearly focused on ensuring that this document was robust and clear for the reader. There was an overt recognition that research recommendations should be organized and described in sufficient detail to ensure that prior to the next update of any anemia guideline, there would be new data addressing gaps in our current knowledge. Thus, there are no concrete research recommendations in this version; they will be published in a separate document in the near future. The intended effect of this change in how the research recommendations are presented is to provide a


*0272-6386/06/4705-0101$32.00/0*
*doi:10.1053/j.ajkd.2006.04.023*

guidepost for funding agencies and investigators to target research efforts in those areas that will provide important information that will benefit patient outcomes.

This final version of the Clinical Practice Guidelines and Recommendations for Anemia has undergone revision in response to comments during the public review, an important and integral part of the KDOQI guideline process. Nonetheless, as with all guideline documents, there is a need for revision in the light of new evidence, and more importantly, a concerted effort to translate the guidelines into practice. Considerable effort has gone into their preparation over the past 2 years, and every attention has been paid to their detail and scientific rigor, no set of guidelines and clinical practice recommendations, no matter how well developed, achieves its purpose unless it is implemented and translated into clinical practice. Implementation is an integral component of the KDOQI process, and accounts for the success of its past guidelines. The Kidney Learning System (KLS) component of the National Kidney Foundation is developing implementation tools that will be essential to the success of these guidelines.

In a voluntary and multidisciplinary undertaking of this magnitude, many individuals make contributions to the final product now in your hands. It is impossible to acknowledge them individually here, but to each and every one of them we extend our sincerest appreciation. This limitation notwithstanding a special debt of gratitude is due to the members of the Work Group, and their co-chairs, David Van Wyck and Kai-Uwe Eckardt. It is their commitment and dedication to the KDOQI process that has made this document possible.

***Adeera Levin, MD***
***KDOQI Chair***

***Michael Rocco, MD***
***KDOQI Vice-Chair***

# EXECUTIVE SUMMARY

## INTRODUCTION

Anemia commonly contributes to poor quality of life (QOL) in patients with chronic kidney disease (CKD). Fortunately, among the disorders that may afflict patients with CKD, anemia is perhaps the most responsive to treatment. Anemia was the subject of one of the first efforts of the National Kidney Foundation (NKF) to improve patient outcomes through the development, dissemination, and implementation of Dialysis Outcomes Quality Initiative (DOQI) Clinical Practice Guidelines.[1] The first update of these guidelines appeared in 2001 under the newly organized NKF-Kidney Disease Outcomes Quality Initiative (KDOQI).[2] In 2004, the NKF-KDOQI Steering Committee appointed a Work Group and Evidence Review Team (ERT) to undertake the first comprehensive revision of the KDOQI Clinical Practice Guidelines for the Management of Anemia in CKD. This Executive Summary provides a brief background description of CKD and anemia, outlines the scope of the guidelines and the methods of evidence review and synthesis, and provides the complete text of the guideline statements.

## BACKGROUND

### *About CKD*

CKD is a worldwide public health issue.[3] In the United States, the incidence and prevalence of kidney failure are increasing (Fig 1), outcomes are poor, and the cost is high.[4] The prevalence of earlier stages of CKD is approximately 100 times greater than the prevalence of kidney failure, affecting almost 11% of adults in the United States.[4,5] There is growing evidence that some of the adverse outcomes of CKD can be prevented or delayed by preventive measures, early detection, and treatment. Strategies to improve outcomes include Clinical Practice Guidelines (CPGs) for CKD[4] and for the management of hypertension,[3] dyslipidemia,[6] bone disease,[7] nutrition,[8] and cardiovascular disease (CVD)[9] in patients with CKD.

### *About Anemia*

Before considering a patient with both anemia and CKD, a brief introduction to the processes that contribute to anemia may be helpful. Anemia is the clinical manifestation of a decrease in circulating red blood cell mass and usually is detected by low blood hemoglobin (Hb) concentration. The cause, treatment, and prognostic significance of anemic disorders vary widely. Causes are distinguished clinically by markers of the magnitude and appropriateness of a marrow response to anemia. Under usual conditions, bone marrow generates approximately 200 billion new cells per day to match the number of senescent cells removed from circulation. The expected compensatory response to anemia is a heightened rate of erythropoiesis. Failure to demonstrate a compensatory response signifies slowed or defective erythropoiesis. Thus, hyperproliferative disorders reflect increased destruction of red blood cells with normal marrow response, whereas hypoproliferative and maturation disorders reflect impaired red blood cell production.

The cellular and molecular biology of erythropoiesis has important implications for understanding, evaluating, and treating anemia in patients with CKD. Effective circulating red blood cell mass is controlled by specialized interstitial cells in the kidney cortex that are exquisitely sensitive to small changes in tissue oxygenation.[11] If tissue oxygenation decreases because of anemia or other causes, these cells sense hypoxia and produce erythropoietin.[12] Within erythroid islands, the autonomous unit of erythropoiesis in marrow, receptors on the surface of the earliest red blood cell progenitors, erythroid colony-forming units (CFU-Es), bind erythropoietin. Binding of erythropoietin to erythropoietin receptors salvages CFU-Es and the subsequent earliest erythroblast generations from preprogrammed cell death (apoptosis), thereby permitting cell survival and division and the eventual expansion of erythropoiesis. If successful, these erythropoietin-stimulated events increase the production of reticulocytes, restore normal circulating red blood cell mass, and correct tissue hypoxia.[13]

In anemic patients, 1 or more steps in this autoregulatory sequence may fail. In the pres-


*0272-6386/06/4705-0102$32.00/0*
*doi:10.1053/j.ajkd.2006.03.010*

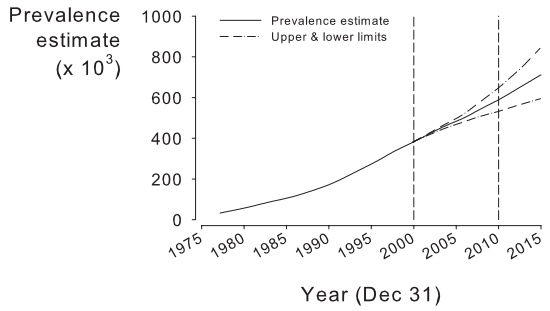


**Fig 1. Kidney failure in the United States. Prevalence estimates of kidney failure treated by dialysis and transplantation (end-stage renal disease [ESRD]) in the United States. Prevalence refers to the number of patients alive on December 31st of the year. Upper and lower estimates reflect the effect of potential changes in ESRD incidence, diabetes prevalence, ESRD death rate, and underlying age and race structure of the US population after the year 2000. Reprinted with permission.[10]**

ence of kidney disease, erythropoietin production may be impaired, leading to erythropoietin deficiency and the apoptotic collapse of early erythropoiesis. If folate and vitamin $B_{12}$ are lacking, deoxyribonucleic acid (DNA) synthesis is impaired, and erythroblasts, normally undergoing rapid division during this period of erythropoiesis, succumb to apoptosis.[13] In ongoing folate or vitamin $B_{12}$ deficiency, disordered DNA synthesis, maturation arrest, and ineffective early erythropoiesis lead to a macrocytic anemia. Conversely, if iron is lacking, the Hb-building steps that follow rapid cell division are affected: synthesis of both heme and globin slow, and erythropoiesis is impaired. Reticulocytes that emerge from marrow are few, poorly hemoglobinized, and small. A hypochromic microcytic anemia eventually results. Inflammation, a disorder common among patients with CKD, appears to impair both the early erythropoietin-dependent period of erythropoiesis and the later iron-dependent period. Inflammatory cytokines inhibit erythropoietin production, directly impair growth of early erythroblasts, and—especially in the absence of erythropoietin—promote death by ligand-mediated destruction of immature erythroblasts.[14] In addition, inflammatory cytokines stimulate hepatic release of hepcidin, which simultaneously blocks iron absorption in the gut and iron release from resident macrophages, prompting a decrease in transferrin saturation (TSAT) and thereby promoting iron-deficiency erythropoiesis.[15] Thus, the anemia of inflammation characteristically is hypoproliferative and not infrequently includes features suggesting iron-deficiency erythropoiesis.

This synopsis provides an introduction to the subject and purpose of the following CPGs for patients with both anemia and CKD. Guideline 1.1 describes identification of the patient with anemia and CKD. Guideline 1.2 describes the recommended initial evaluation; Guideline 2.1, the goal of treatment; and Guidelines 3.1, 3.2, and 3.3, the use of therapeutic agents.

## SCOPE OF THE GUIDELINES

New findings, new agents, and the need for an expanded scope prompt the need for a comprehensive revision of existing NKF-KDOQI CPGs for the Treatment of Anemia in CKD. In preparing the current guidelines, the Anemia Work Group members broadened our inquiry to include all stages of CKD, identify areas of concern to current practitioners, adopt a structured intensive evidence review process not previously used, apply that process to both newly available literature and literature examined in the development of previous guideline versions, formulate conclusions that distinguish *evidence-based guidelines* from *expert-opinion–based clinical practice recommendations* (CPRs), and present both guidelines and recommendations in a new format to more clearly describe what is not known. To ensure that the next update profits from evidence we currently lack, we identified limitations of currently available evidence and, in a subsequent report, will identify priorities for needed research.

### *Intended Reader*

Our intended reader is the practitioner who manages patients with CKD, including nephrologists, primary-care providers, cardiologists, nurse practitioners, nurses, and dietitians. Clinical pharmacists, quality outcomes directors, and clinical investigators will find the document useful. We write primarily for practitioners in North America. Nevertheless, from the onset, we have coordinated our efforts with guideline development processes

elsewhere, ensured that Work Group membership includes experts from Latin America and Europe, and planned so that this document may serve as the last of the KDOQI Anemia Guidelines and a foundation for the first truly global guideline under the auspices of the Kidney Disease: Improving Global Outcomes (KDIGO) initiative (www.kdigo.org).

### *Scope*

We address the target population of patients with CKD stages 1 to 5 not on dialysis therapy, on hemodialysis (HD) or peritoneal dialysis (PD) therapy, or with a kidney transplant in the full range of practice settings in which they are encountered. However, the evidence continues to derive disproportionately from findings in facility-based HD patients. We have not been unmindful of cost implications. However, net medical benefit to the patient is the foundation of each of our guidelines and recommendations. Our commitment, in short, is to assist practitioners in the care of patients by describing best practice and the evidence for it. In this way, individual practitioners who face local reimbursement constraints may make informed decisions armed with appropriate facts. Similarly armed, those responsible for guiding reimbursement policy may make informed decisions consistent with the evidence.

### *Evidence, Opinion, Guidelines, and Recommendations*

When the quality of evidence is high or moderately high, we present a CPG based on evidence, rate the quality of that evidence, and distinguish the evidence-based guideline by enclosing it in a text box. When the quality of evidence is low, very low, or missing, but the topic is important to practitioners, we offer a CPR and cite limitations to the current literature. In a subsequent document, we will propose and prioritize needed research. Throughout this document, a text box surrounds each evidence-based guideline, and the strength of the guideline is rated as "strong" or "moderately strong." The phrase, "In the opinion of Work Group members" precedes each CPR. Distinguishing evidence-based guidelines from CPRs is in keeping with recent advances in KDOQI policy and practice.

*The overall strength of each guideline statement was rated by assignment as either strong or moderately strong. A strong rating indicates "it is strongly recommended that clinicians routinely follow the guideline for eligible patients. There is high-quality evidence that the practice results in net medical benefit to the patient." The moderately strong rating indicates "it is recommended that clinicians routinely follow the guideline for eligible patients. There is at least moderately high-quality evidence that the practice results in net medical benefit to the patient." Overall, the strength of the guidelines and recommendations was based on the extent to which the Work Group could be confident that adherence will do more good than harm. Strong guidelines require support by evidence of high quality. Moderately strong guidelines require support by evidence of at least moderately high quality. Incorporation of additional considerations modified the linkage between quality of evidence and strength of guidelines, usually resulting in a lower strength of the recommendation than would be supportable based on the quality of evidence alone.*

Our objective is to describe the evidence base for key elements in the identification, evaluation, and management of patients with CKD-associated anemia. For topics on which we undertook a systematic literature review, we present detailed information, usually in the form of summary evidence tables. These topics include Hb thresholds for initiating therapy, Hb level therapeutic goals, iron status goals, or efficacy of adjuvants in achieving Hb goals. Results that bear directly on patient lives (mortality, morbidity, QOL, and adverse events [AEs]) receive particular attention. Topics for which the evidence base is limited deserve brief mention and receive it. Information that involves implementation, application, or protocol development, we leave to the NKF Kidney Learning System (KLS) resources.

When the quality of evidence is low, we will follow acknowledgement of these limitations in a separate publication by encouraging further investigation.

### *Relationship to Previous Guidelines*

The lineage of the current document derives from both the most recent (2001) version of the

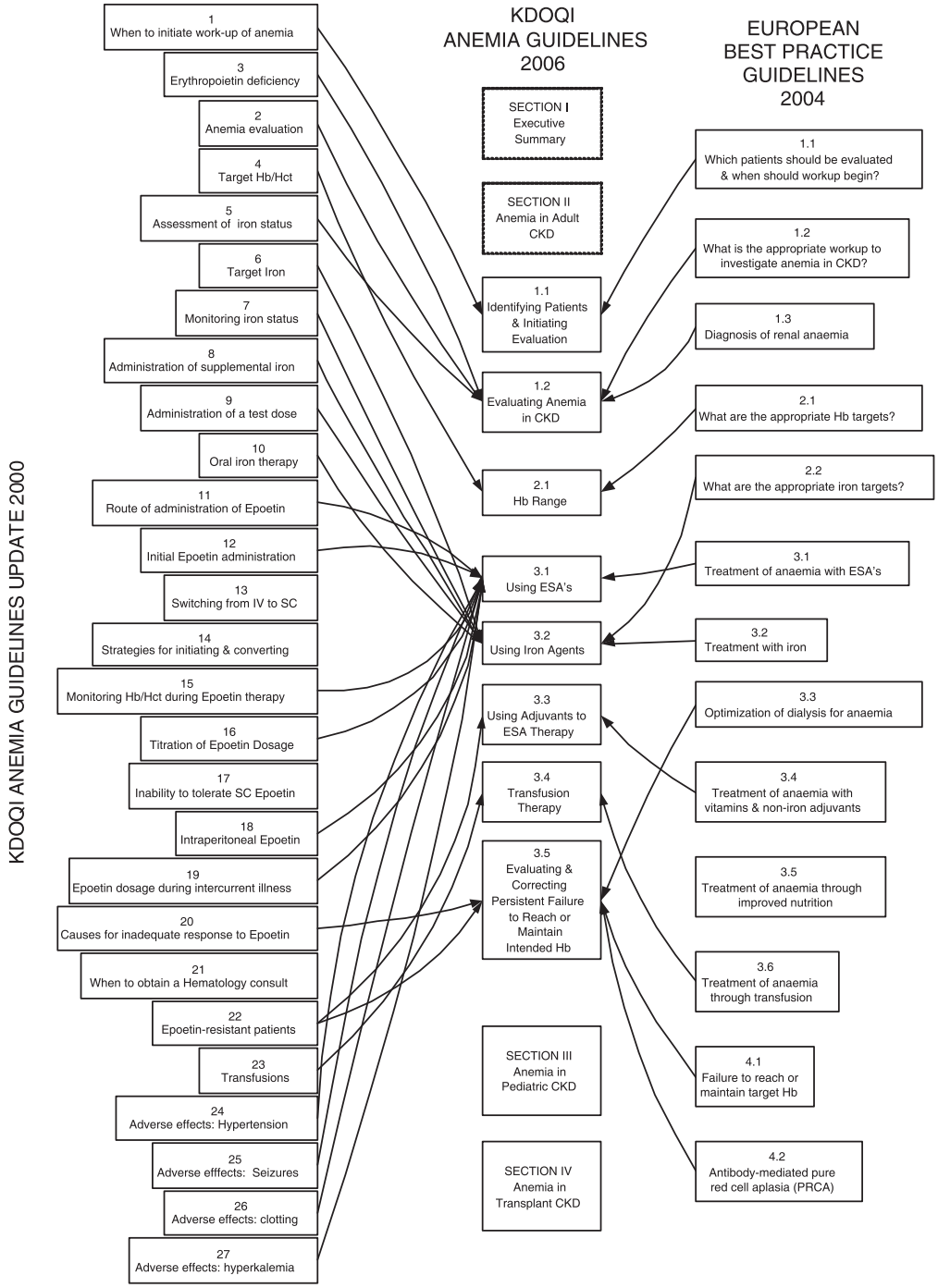


**Fig 2. Relationship between current and previous anemia guidelines.**

KDOQI Guidelines for Anemia[2] and the most recent (2004) version of the European Best Practices Guidelines (EBPGs) for anemia (Fig 2).[16] Our intention is to simplify the current guidelines into sections on identification, definition, and evaluation of anemia (Guideline 1.1 and 1.2); Hb treatment target (Guideline 2.1); and management (Guidelines 3.1-4.1), with parallel

**Table 1. Key Differences between Current Guidelines (KDOQI Anemia 2006) and Previous Anemia Guidelines (KDOQI 2000 and EBPG 2004)**

| Topic | KDOQI 2000 Anemia Guideline | EBPG 2004 Anaemia Guideline | KDOQI 2006 Anemia Guideline | Reason KDOQI 2006 Differs from Prior Guidelines |
|---|---|---|---|---|
| Definition of Anemia by Hb | <12.0 g/dL in males and postmenopausal females<br><11.0 g/dL in premenopausal females and prepubertal patients | <12.0 g/dL males<br><11.0 g/dL females | <13.5 g/dL males<br><12.0 g/dL females | KDOQI 2006 uses more recent NHANES data set, defines anemia as any Hb below the 5th percentile for the adult, gender-specific population. Among males, no adjustment is made for age >70 years, to exclude the possibility that pathological conditions contribute to lower Hb values. Among females, the 5th percentile determination is made only among individuals without evidence of iron deficiency, as defined by TSAT <16% or ferritin <25 ng/mL. |
| Target Hb | 11-12 g/dL | >11.0 g/dL target<br>>12.0 in CVD not recommended<br>Hb >14.0 g/dL not desirable | ≥11 g/dL, caution when intentionally maintaining Hb >13 g/dL | Current guideline reflects QOL benefits at Hb maintained ≥11.0 g/dL, risks when intentionally maintaining Hb >13.0, and recognition that Hb will often exceed 13 g/dL unintentionally, without evidence of increased risk, in patients with Hb intent to treat ≥11.0 g/dL. |
| Target Iron Status | TSAT (%)<br>lower limit: 20<br>upper limit: 50<br><br>Ferritin (ng/mL)<br>lower limit: 100 | TSAT (%)<br>lower limit: 20<br>target: 30-50<br><br>Ferritin (ng/mL)<br>lower limit: 100<br>target: 200-500 | TSAT (%)<br>lower limit ≥20<br><br>Ferritin (ng/mL)<br>lower limit: 200 HD-CKD<br>100 non-HD-CKD<br>> 500 not routinely recommended | TSAT:<br>Current guideline reflects unchanged lower bound for iron therapy; upper limit of TSAT not specified.<br><br>Ferritin:<br>Current guideline distinguishes HD- from non–HD-CKD on basis of available evidence. Lower limit sets objective of iron therapy. There is insufficient evidence to assess harm and benefit in maintaining ferritin > 500 ng/mL . In HD-CKD, 200 ng/mL reflects evidence for substantial efficacy of IV iron at ferritin <200 ng/mL. |
| Adjuvants | | | | |
| L-Carnitine | Not recommended | Not recommended for general use | Not routinely recommended | Current guideline based on low-quality evidence which shows lack of efficacy |
| Ascorbate | | | Not routinely recommended | Current guideline reflects combination of safety concerns and low quality evidence of efficacy |
| Androgens | | Selective use | Not recommended | Current guideline reflects serious safety concerns. Evidence for efficacy is low quality,. |

organization for pediatrics. Key differences between current and past guidelines are set out in Table 1.

## OPERATING DEFINITIONS

***Erythropoiesis-stimulating agent (ESA):*** The term ESA applies to all agents that augment erythropoiesis through direct or indirect action on the erythropoietin receptor. Currently available ESAs include epoetin alfa, epoetin beta, and darbepoetin alfa.

***Therapeutic goal:*** A therapeutic goal is the intended goal of current therapy, not the current result of previous therapy. This definition applies equally to therapeutic goals for both Hb and iron.

### *Indicators of Efficacy*

***Efficacy of anemia management:*** Efficacy of anemia management is indicated in a single patient by an Hb level greater than the target threshold, and in a group of patients, by the percentage of patients maintained at greater than target threshold.

***ESA efficacy:*** ESA efficacy is indicated by the dose of ESA needed to achieve or maintain Hb levels at greater than the target threshold.

***Adjuvant efficacy:*** Adjuvant efficacy is indicated by the percentage of patients who successfully exceed the target Hb threshold or achieve an increase in Hb level greater than 1 g/dL without initiating ESA therapy or increasing ESA doses to greater than baseline. Among patients with steady-state Hb levels greater than target threshold, adjuvant efficacy is indicated by ESA dose reduction.

# II. CLINICAL PRACTICE GUIDELINES AND CLINICAL PRACTICE RECOMMENDATIONS FOR ANEMIA IN CHRONIC KIDNEY DISEASE IN ADULTS

# CPR 1.1. IDENTIFYING PATIENTS AND INITIATING EVALUATION

Identifying anemia is the first step in evaluating the prognostic, diagnostic, and therapeutic significance of anemia in the patient with CKD.

**1.1.1 Stage and cause of CKD:**
**In the opinion of the Work Group, Hb testing should be carried out in all patients with CKD, regardless of stage or cause.**

**1.1.2 Frequency of testing for anemia:**
**In the opinion of the Work Group, Hb levels should be measured at least annually.**

**1.1.3 Diagnosis of anemia:**
**In the opinion of the Work Group, diagnosis of anemia should be made and further evaluation should be undertaken at the following Hb concentrations:**

- **<13.5 g/dL in adult males.**
- **<12.0 g/dL in adult females.**

## BACKGROUND

Anemia develops early in the course of CKD and is nearly universal in patients with CKD stage 5.[17] The purpose of specifying Hb level thresholds to define anemia is to identify patients who are most likely to show pathological processes contributing to a low Hb level and who therefore are most likely to benefit from further anemia evaluation. Thus, the current guideline (Guideline 1.1) identifies Hb level thresholds that should trigger diagnostic evaluation (Guideline 1.2). Conversely, Hb levels that should trigger ESA therapy are defined in Guideline 2.1.

## RATIONALE

### *Stage and Cause of CKD*

***Hb testing should be carried out in all patients with CKD, regardless of stage or cause.*** Anemia is associated with CKD of any cause,[18-22] including transplant-associated CKD (see Guideline 4.1). The severity of anemia in patients with CKD is related to both the degree of loss of glomerular filtration rate (GFR) and the cause of kidney disease. The lowest Hb levels are found in anephric patients and those who commence dialysis therapy at very low levels of kidney function.[23,24]

The reported prevalence of anemia by CKD stage depends in large part on the size of the study; whether study participants are selected from the general population, are at high risk for CKD, or are patients already under a physician's care; what level of Hb is defined as constituting anemia; and whether patients do or do not have diabetes.

Studies reviewed for the purposes of guideline statement 1.1.1 include those of patients with CKD before dialysis therapy, those with kidney transplants, and those on dialysis therapy. The reviewed literature spans close to 40 years of investigation up to the year 2000 and describes clinical findings of researchers as they explore the relationships between Hb level or hematocrit (Hct) and kidney function (Table 2 and 3). The majority of available data were derived from studies of small sample size, most of which are cross-sectional studies, or baseline data from clinical trials of variable size and robustness.

In 12 of the 21 studies reviewed, there was an association between level of Hb or Hct and the selected measure of kidney function. They also demonstrate variability in levels of Hb or Hct at each level of kidney function, whether assessed by using serum creatinine ($S_{Cr}$) concentration, creatinine clearance ($C_{Cr}$), or estimated GFR (eGFR). However, the consistency of the information they provide indicates a trend toward lower Hb levels at lower levels of GFR and variability in Hb levels across GFR levels.

More recent studies used large databases to examine the relationship between Hb level or Hct and kidney function (Table 4). A cross-sectional analysis examined 12,055 ambulatory adult patients (≥18 years of age) who had at least 2 $S_{Cr}$ measurements 2 years apart and at least 1 Hct measurement and weight recorded between 1990 and 1998.[25] Results should progressively lower Hct at an estimated $C_{Cr}$ less than 60 mL/min/1.73 $m^2$ in men and 40 mL/min/1.73 $m^2$ in women (Table 5). When GFR normalized to body surface area (BSA) was estimated by using the Modification of Diet in Renal Disease (MDRD) equation, both men and women

**Table 2. Relationship Between Hb Level and Kidney Function**

| Author, Year | No. of Subjects | Applicability | GFR Range (mL/min/1.73 m²) 0 30 60 90 120 | Results*/ Mean Level | Quality |
|---|---|---|---|---|---|
| Levin,[288] 1999 | 318 | ⬆⬆⬆ | | ⬆ | ● |
| Taralov,[289] 1998 | 63 | ⬆⬆ | $S_{Cr}$ 5.1 mg/dL | ⬆ | ● |
| Clyne,[292] 1993 | 58 | ⬆⬆ | | ⇧ | ● |
| Ishimura,[291] 1998 | 40 | ⬆⬆ | $S_{Cr}$ 2–8 mg/dL | ⬆ | ● |
| Nankivell,[141] 1995 | 123 | ⬆ | | ⬆ | ○ |
| de Klerk,[292] 1982 | 99 | ⬆ | | ⇧ | ○ |
| Urabe,[293] 1987 | 17 | ⬆ | $S_{Cr}$ 7–15 mg/dL | ⇔ | ○ |
| Silverberg,[294] 1996 | 33 | ⬆⬆ | | 10.0 g/dL | ● |
| Lin,[295] 1996 | 51 | ⬆⬆ | | 12.5 g/dL | ○ |
| Clyne,[296] 1994 | 12 | ⬆ | | 8.9 g/dL | ○ |
| Portoles,[297] 1997 | 11 | ⬆ | | 9.0 g/dL | ○ |
| Dimitrakov,[298] 1994 | 6 | ⬆ | $S_{Cr}$ 4.5±0.4 mg/dL | 7.6 g/dL | ○ |

Unshaded studies reported the strength of association between the outcome measure (in this case, hemoglobin) and kidney function; shaded studies reported mean or median levels of the outcome measure in the study sample.

* ⬆ = higher GFR associated with higher hemoglobin (statistically significant);
⇧ = higher GFR associated with higher hemoglobin;
⇔ = GFR *not* associated with hemoglobin.

Reprinted with permission.[4]
The reference numbers in the table relate to the numbering of references in the CKD Guidelines (reference 4). The articles are also referenced in the bibliography of this guideline under references 30, 33, 66-75.

developed a statistically significant decrease in Hct at the same BSA-normalized GFR, 50 mL/min/1.73 $m^2$. This relationship persisted when analyses were restricted to patients who were normochromic and normocytic, ie, presumably non–iron deficient. However, the change in age- and race-adjusted Hct with decreasing levels of GFR was greater in men than women. It should be noted that only 10% of men and 6% of women had an eGFR of 50 mL/min/1.73 $m^2$ or less (MDRD formula), and the indications for measuring $S_{Cr}$ and Hct were unknown.

Two studies examined the relationship between prevalent Hb concentration and GFR by using results from the National Health and Nutrition and Examination Survey (NHANES) III database. NHANES III is a cross-sectional survey of nutritional and health status in 15,419 individuals randomly selected from the general US population from 1988 to 1994. Results from NHANES III[26,27] are consistent with those obtained in ambulatory adult patients (Table 6).[25] At an eGFR less than 75 mL/min/1.73 $m^2$ in men and 45 mL/min/1.73 $m^2$ in women, the associated Hb level is lower than that seen at eGFRs above those thresholds (Fig 3). The relationship is observed best in the distribution of the lowest fifth percentile of Hb levels. In general, the lower the eGFR at less than the respective threshold, the lower the associated Hb level, but confidence intervals (CIs) are broad at the lowest eGFR levels because the number of observed individuals with a low eGFR is small. For example, only 3.5% of women and 1.4% of men in the survey showed an eGFR of 30 mL/min/1.73 $m^2$ or less.

The relationship between GFR and prevalence of anemia is determined in large part by the Hb concentration used to define anemia. In NHANES III, prevalence of a Hb level less than 13 g/dL increases at less than a threshold eGFR of 60 mL/min/1.73 $m^2$ in males and 45 mL/min/1.73 $m^2$ in females (Fig 4). However, the prevalence of a Hb level less than 11 g/dL is not greater than reference except at an eGFR less than 30 mL/min/1.73 $m^2$ in both males and females. Again, precise estimates of prevalence are limited by rela-

**Table 3. Relationship Between Hct and Kidney Function**

| Author, Year | No. of Subjects | Applicability | GFR Range (mL/min/1.73 m²) 0 30 60 90 120 | Results*/ Mean Level | Quality |
|---|---|---|---|---|---|
| Klahr,[289] 1995 | 840 | ††† | | ⬆ | ○ |
| Radtke,[290] 1979 | 194 | †† | | ⬆ | ○ |
| Howard,[291] 1989 | 106 | †† | | ⬆ | ○ |
| Lim,[301] 1990 | 26 | †† | $S_{Cr}$ 2–12 mg/dL | ⬆ | ○ |
| Besarab,[292] 1985 | 102 | † | $S_{Cr}$ 1.5–2.1 mg/dL | ⇧ | ○ |
| Brod,[293] 1967 | 17 | † | | ⇧ | ○ |
| Urabe,[295] 1987 | 17 | † | $S_{Cr}$ 7–15 mg/dL | ⇔ | ○ |
| Silverberg,[294] 1996 | 33 | †† | | 30% | ○ |
| Roth,[304] 1994 | 83 | † | | 27% | ○ |
| Kuriyama,[305] 1997 | 66 | †† | | 32% | ○ |
| Lin,[295] 1996 | 51 | †† | | 35% | ○ |
| Portoles,[297] 1997 | 11 | † | | 26% | ○ |
| Hayashi,[306] 2000 | 9 | † | $S_{Cr}$ 6.2 ±0.7 mg/dL | 24% | ○ |
| Schwartz,[307] 1991 | 7 | † | | 29% | ○ |
| Dimitrakov,[299] 1994 | 6 | † | $S_{Cr}$ 4.5 ±0.4 mg/dL | 23% | ○ |

* ⬆ = higher GFR associated with higher hematocrit (statistically significant);
⇧ = higher GFR associated with higher hematocrit;
⇔ = GFR *not* associated with hematocrit.

Reprinted with permission.[4]
The reference numbers in the table relate to the numbering of references in the CKD Guidelines (reference 4). The articles are also referenced in the bibliography of this guideline under references 30, 33, 60-75.

tively small numbers; in particular, less than a GFR of 30 mL/min/1.73 $m^2$ (N = 52).

The relationship between prevalence of anemia and GFR may be changing as a result of earlier identification and treatment of anemia. Comparing results of NHANES III with NHANES IV shows a lower prevalence of anemia for each CKD stage in the more recent survey (Fig 5).[28] In this analysis, anemia was defined by World Health Organization (WHO) criteria (Hb level < 12 g/dL in women and < 13 g/dL in men).

The prevalence of anemia among patients is much greater than that observed among individuals randomly surveyed in the general population. In a cross-sectional study of 5,222 adult patients with CKD who were selected from 237 US physician practices (including family practice, internal medicine, nephrology, and endocrinology), mean Hb levels for an MDRD eGFR of 60 or greater (CKD stages 1 and 2), 30 to 59 (CKD stage 3), 15 to 29 (CKD stage 4), and less than 15 mL/min/1.73 $m^2$ (CKD stage 5) were 12.8 ± 1.5, 12.4 ± 1.6, 12.0 ± 1.6, and 10.9 ± 1.6 g/dL, respectively.[29] The prevalence of untreated anemia (defined as a Hb level < 12, 10 to 12, and < 10 g/dL) for different CKD stages (Fig 6) is much greater than that reported in NHANES surveys.[26,27] A greater disease burden among patients compared with randomly selected individuals provides a likely explanation for these findings.

Because data points at GFR levels less than 30 mL/min/1.73 $m^2$ were scarce in all except the previous cross-sectional study,[29] the Canadian Multicentre Study[30] was used to demonstrate trends in a large cohort of patients before dialysis therapy (Fig 7). The prevalence of anemia was greatest at the lowest levels of GFR, but approached 20% among patients with a GFR of 30 to 44 mL/min/1.73 $m^2$ (Fig 8). Similarly, in another study of 131,848 patients who began dialysis therapy in the United States between 1995 and 1997, proportions of patients with Hcts less than 30% and less than 36% immediately before the initiation of dialy-

**Table 4. Prevalence of Anemia by Level of Kidney Function**

| Author, Year | N | Definition of Anemia Hb (g/dL) | Applicability | Level of Kidney Function | Prevalence of Anemia | | Results | Quality |
|---|---|---|---|---|---|---|---|---|
| | | | | | Diabetic | Nondiabetic | | |
| El-Achkar, 2005 [37] | 5,380 | Men & Women >50 yr, Hb <12; Women ≤50 yr, Hb <11 | | GFR ≥89 | 8.7% | 6.9% | ⬆ | ● |
| | | | | GFR 60-89 | 7.5% | 7% | | |
| | | | | GFR 30-59 | 22.2% | 7.9% | | |
| | | | | GFR <30 | 52.4% | 50% | | |
| | | | | | (Likelihood [%] of Hb level <12 g/dL) [a] | | | |
| | | | | | Men | Women | | |
| Hsu, 2002 [26] | 15,971 | Men Hb 10-12 Women Hb10-12 | | $Cr_{Cl}$ >80 | 3% | 7% | ⬆ | ◎ |
| | | | | $Cr_{Cl}$ 41-50 | 4% | 10% | | |
| | | | | $Cr_{Cl}$ 21-30 | 12% | 25% | | |
| Astor, 2002 [27] | 15,419 | Men Hb <12 [b] Women Hb <11 | | GFR ≥90 | 1.8% | | ⬆ | ◎ |
| | | | | GFR 60-89 | 1.3% | | | |
| | | | | GFR 30-59 | 5.2% | | | |
| | | | | GFR 15-29 | 44.1%[c] | | | |
| | | | | | Men | Women | | |
| Hsu, 2001 [25] | 8,220 | Hb <11 | | GFR >41-50 | 9% (7/77) | 5% (18/333) | ⬆[d] | ◎ |
| | | | | GFR 31-40 | 10% (3/29) | 10% (12/116) | | |
| | | | | GFR 20-30 | 0% (0/17) | 33% (9/27) | | |
| | | | | GFR ≤20 | 60% (12/20) | 52% (11/21) | | |
| McClellan, 2004 [29] | 5,222 | Hb <12 | | GFR ≥60 | 26.7% | | ⬆ | ◎ |
| | | | | 60> GFR ≥30 | 41.6% | | | |
| | | | | 30> GFR ≥15 | 53.6% | | | |
| | | | | GFR <15 | 75.5% | | | |
| Fehr, 2004 [85] | 4,760 | Hb <11 | | $Cr_{Cl}$ >90 [e] | <1% | | ⬆ | ○ |
| | | | | $Cr_{Cl}$ 60-89 | <2% | | | |
| | | | | $Cr_{Cl}$ 40-59 | ~3% | | | |
| | | | | $Cr_{Cl}$ 20-39 | ~15% | | | |
| | | | | $Cr_{Cl}$ <20 | ~38% | | | |

Footnotes:
a. Data given for age 61-70 and Hb <12 g/dL.
b. To focus on clinically significant and potentially treatable anemia, a more stringent definition (Hb <12 for men, Hb <11 for women) was used for most analyses. However, in analysis using the WHO definition (Hb <13 for men and Hb <12 for women) the overall prevalence for men was 3.5% vs. women 10.7%.
c. All prevalence rates adjusted for age = 60. This corresponds to approximately 160,000 (SE 44,000) noninstitutionalized civilians in the US in 1991.
d. At any given level of $Cr_{Cl}$, men had steeper slope of decrease in Hb, as did blacks> Mexican >whites, older vs. younger men, and younger vs. older women.
e. No statistical pooling between categories of creatinine clearance stages.

Coding of Outcome:
⬆ statistically significant increase in anemia with decreasing kidney function.

sis therapy were 67.5% and 93%, respectively.[31]

Patients with diabetes are more prone to both develop anemia and develop anemia at earlier stages of CKD than their nondiabetic counterparts (Fig 9).[32-37] In a cross-sectional clinical audit of 820 Australian patients with diabetes, anemia was 2 to 3 times more prevalent in patients with diabetes compared with the general population at all levels of GFR (Fig 9). In an extension of the same audit, patients with type 2 diabetes with a $C_{Cr}$ of 60 to 90 mL/min/1.73 $m^2$ were twice as likely to have anemia than those with a $C_{Cr}$ greater than 90 mL/min/1.73 $m^2$. Patients with diabetes with a $C_{Cr}$ less than 60 mL/min/1.73 $m^2$ were twice as likely to have anemia as those with a $C_{Cr}$ of 60 to 90 mL/min/1.73 $m^2$.[36] In the Kidney Early Evaluation Program (KEEP 2.0), a cross-sectional community-based screening program aimed at detecting CKD

**Table 5. Difference in Hb and Hct From Reference by Category of $C_{Cr}$**

| | Women ($N$ = 8,495) | | | | Men ($N$ = 3,560) | | | |
|---|---|---|---|---|---|---|---|---|
| (reference group is $C_{Cr}$ > 80 mL/min) | Difference in hematocrit | | Difference in hemoglobin | | Difference in hematocrit | | Difference in hemoglobin | |
| | % | *P* value | g/dL | *P* value | % | *P* value | g/dL | *P* value |
| 80 ≥ $C_{Cr}$ > 70 mL/min | −0.0 (−0.2, 0.2) | 0.96 | −0.0 (−0.1, 0.1) | 0.72 | −0.3 (−0.7, 0.1) | 0.14 | −0.1 (−0.3, −0.0) | 0.03 |
| 70 ≥ $C_{Cr}$ > 60 mL/min | −0.1 (−0.3, 0.1) | 0.41 | −0.0 (−0.1, 0.0) | 0.39 | −0.2 (−0.7, 0.2) | 0.32 | −0.1 (−0.2, 0.1) | 0.31 |
| 60 ≥ $C_{Cr}$ > 50 mL/min | −0.2 (−0.4, 0.1) | 0.26 | −0.1 (−0.2, 0.0) | 0.17 | −1.0 (−1.5, −0.5) | 0.0002 | −0.4 (−0.6, −0.2) | <0.0001 |
| 50 ≥ $C_{Cr}$ > 40 mL/min | −0.3 (−0.6, 0.1) | 0.10 | −0.1 (−0.2, 0.0) | 0.03 | −2.4 (−3.1, −1.7) | <0.0001 | −0.9 (−1.2, −0.7) | <0.0001 |
| 40 ≥ $C_{Cr}$ > 30 mL/min | −1.7 (−2.1, −1.3) | <0.0001 | −0.6 (−0.8, −0.5) | <0.0001 | −3.7 (−4.6, −2.8) | <0.0001 | −1.4 (−1.7, −1.1) | <0.0001 |
| 30 ≥ $C_{Cr}$ > 20 mL/min | −2.9 (−3.5, −2.3) | <0.0001 | −1.0 (−1.2, −0.8) | <0.0001 | −3.5 (−4.7, −2.2) | <0.0001 | −1.3 (−1.7, −0.8) | <0.0001 |
| $C_{Cr}$ ≤ 20 mL/min | −6.3 (−7.4, −5.3) | <0.0001 | −2.2 (−2.6, −1.9) | <0.0001 | −10.0 (−11.5, −8.5) | <0.0001 | −3.6 (−4.1, −3.0) | <0.0001 |

Coefficients shown are from age- and race-adjusted sex-stratified models, and values in parentheses are 95% CI for parameter estimates.

Reference group = $C_{Cr}$ >80 mL/min.
Reprinted with permission.[25]

**Table 6. Difference in Hb and Hct From Reference According to Category of BSA and Normalized eGFR**

| (reference group is GFR > 80 mL/min/1.73 m²) | Women (*N* = 8,495) | | | | Men (*N* = 3,560) | | | |
|---|---|---|---|---|---|---|---|---|
| | Difference in hematocrit | | Difference in hemoglobin | | Difference in hematocrit | | Difference in hemoglobin | |
| | % | *P* value | g/dL | *P* value | % | *P* value | g/dL | *P* value |
| 80 ≥ GFR > 70 mL/min/1.73 m² | 0.6 (0.3, 0.8) | <0.0001 | 0.1 (0.1, 0.2) | <0.0001 | 0.1 (−0.2, 0.4) | 0.52 | 0.0 (−0.1, 0.2) | 0.44 |
| 70 ≥ GFR > 60 mL/min/1.73 m² | 0.5 (0.3, 0.7) | <0.0001 | 0.1 (0.1, 0.2) | 0.0009 | 0.1 (−0.2, 0.5) | 0.51 | 0.1 (−0.1, 0.2) | 0.40 |
| 60 ≥ GFR > 50 mL/min/1.73 m² | 0.5 (0.3, 0.8) | <0.0001 | 0.1 (0.0, 0.2) | 0.006 | 0.4 (−0.9, −0.0) | 0.07 | 0.2 (−0.3, 0.0) | 0.07 |
| 50 ≥ GFR > 40 mL/min/1.73 m² | −0.6 (−1.0, −0.2) | 0.002 | −0.2 (−0.4, −0.1) | 0.0004 | −2.0 (−2.8, −1.3) | <0.0001 | −0.8 (−1.1, −0.5) | <0.0001 |
| 40 ≥ GFR > 30 mL/min/1.73 m² | −1.6 (−2.1, −1.0) | <0.0001 | −0.6 (−0.8, −0.3) | <0.0001 | −4.4 (−5.5, −3.2) | <0.0001 | −1.4 (−1.8, −1.0) | <0.0001 |
| 30 ≥ GFR > 20 mL/min/1.73 m² | −3.8 (−4.8, −2.8) | <0.0001 | −1.4 (−1.8, −1.1) | <0.0001 | −5.3 (−6.6, −4.0) | <0.0001 | −1.9 (−2.3, −1.4) | <0.0001 |
| GFR ≤ 20 mL/min/1.73 m² | −5.3 (−6.3, −4.3) | <0.0001 | −1.9 (−2.3, −1.6) | <0.0001 | −9.4 (−10.8, −8.0) | <0.0001 | −3.4 (−3.9, −2.9) | <0.0001 |

Coefficients shown are from age- and race-adjusted sex-stratified models, and values in parentheses are 95% CI for parameter estimates.

Reference group = eGFR >80 mL/min.
Reprinted with permission.[25]

among high-risk patients (those with diabetes, hypertension, or a family history of kidney disease), the prevalence of anemia at each level of eGFR from patients with CKD stages 2 through 5 was greater than in patients without diabetes: 8.7% versus 6.9% in stage 2 ($P$ = not significant [NS]), 7.5% versus 5.0% in stage 3 ($P = 0.015$), 22.2% versus 7.9% in stage 4 ($P < 0.001$), and 52.4% versus 50% in stage 5 ($P = 0.88$).[37]

The following conclusions can be drawn from these studies: (1) the prevalence of anemia at higher levels of GFR (CKD stages 1 and 2) is relatively low in individuals randomly selected from the general population, but is not uncommon in patients with CKD under the care of a physician or identified by virtue of being at high risk for CKD; (2) among individuals from a general population, mean Hb levels decrease and anemia develops consistently only when GFR is less than 60 mL/min/1.73 m$^2$ (stage 3 CKD); (3) the prevalence of anemia increases at later stages of CKD (CKD stages 4 and 5); (4) there is significant variability in Hb levels at any given level of kidney function;

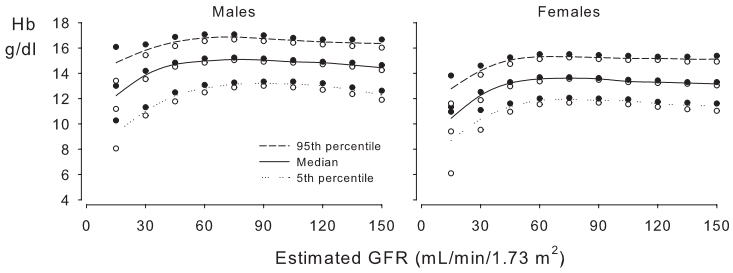


**Fig 3. Relationship between Hb level and eGFR. Data represent a cross-sectional survey of individuals randomly selected from the general US population (NHANES III). Median and 95% confidence limits around the 95th and 5th percentiles are shown for males and females at each eGFR interval. Adapted with permission.[27]**

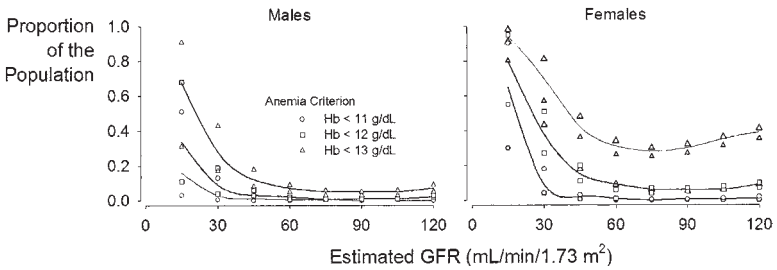


**Fig 4. Relationship between eGFR and prevalence of anemia as defined by differing Hb levels for (A) males and (B) females. Data from NHANES III. Reprinted with permission.[27]**

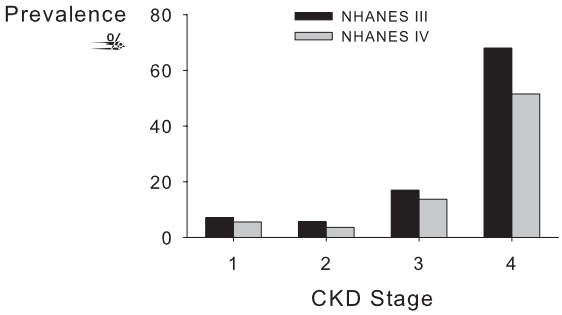


**Fig 5. Prevalence of anemia by CKD stage. Anemia, defined as an Hb level less than 13.0 g/dL in males and less than 12.0 g/dL in females, was plotted by stage of CKD in results from NHANES III compared with NHANES IV. USRDS 2004.[28]**

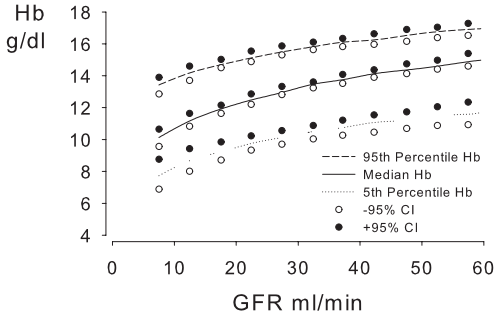


**Fig 7. Hb percentiles by GFR in the Canadian Multicentre Longitudinal Cohort Study. Patients were referred to nephrologists between 1994 and 1997. Results shown exclude patients receiving ESA therapy or with an arteriovenous fistula. Reprinted with permission.[4,30]**

and (5) anemia among patients with diabetes compared with patients without diabetes is more prevalent, more severe, and occurs earlier in the course of CKD.

These observations underscore the need to measure Hb levels in every patient with CKD, regardless of stage or cause.

### *Frequency of Hb Testing in Patients With CKD*

***Hb levels should be measured at least annually.*** Because little is known about the natural history of anemia in patients with CKD, precise information is unavailable to determine the optimum frequency of Hb testing in patients with CKD. The recommendation that patients be evaluated at least annually rests on observations from clinical trials that (in the absence of ESA therapy) the natural history of anemia in patients with CKD is a gradual decline in Hb levels over time.[38,39] In 1 trial,[39] patients assigned to the lower Hb target (9.5 to 10.5 g/dL) entered the trial with Hb values greater than target (mean, 11.8 g/dL) and received ESA only if Hb levels subsequently decreased. During 2 years, a significant proportion of patients eventually required ESA therapy. However, among those who did not require ESA therapy, mean Hb values remained relatively stable (Fig 10). This evidence suggests the need for regular surveillance of Hb levels in patients with CKD without ESA therapy. The statement *Hb levels should be measured at least annually* emphasizes that more frequent Hb surveillance likely will be needed for selected patients, including those with greater disease burden, unstable clinical course, or evidence of previous Hb level decline. Frequency of Hb testing in patients already undergoing ESA therapy is addressed in Guideline 3.1.1.

### *Diagnosis of Anemia*

Diagnosis of anemia should be made and further evaluation should be undertaken at Hb concentrations less than 13.5 g/dL in adult males and less than 12.0 g/dL in adult females. The recommended thresholds for defining anemia

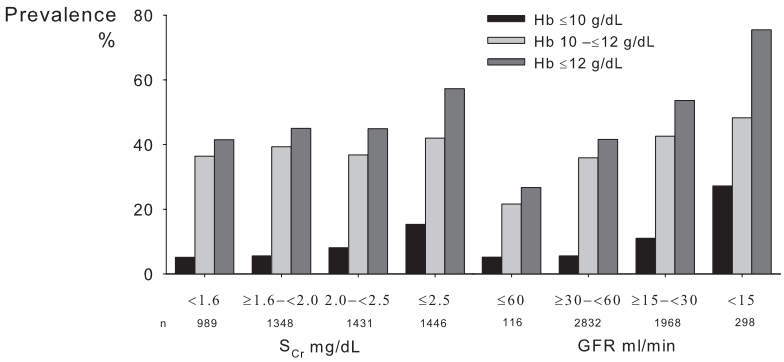


**Fig 6. Relationship between level of renal function, reflected by $S_{Cr}$ level or GFR, and prevalence of anemia, defined at different Hb cutoff levels, among patients under the care of physicians. Reprinted with permission.[29]**

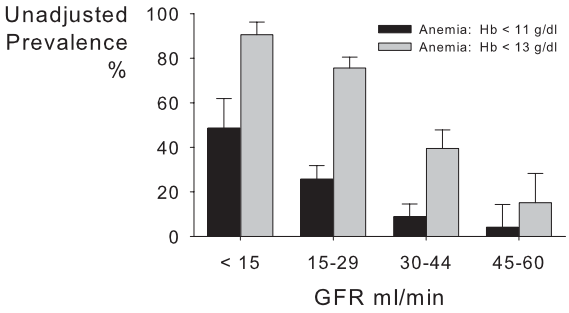


**Fig 8. Prevalence of low Hb level by category of GFR in the Canadian Multicentre Longitudinal Cohort Study. Reprinted with permission.[4,30]**

represent the mean Hb of the lowest fifth percentile of the sex-specific general adult population (Table 7 and 8; Fig 11).[40,41] The conclusion that anemia therefore is defined as a Hb level less than 13.5 g/dL in adult males and less than 12 g/dL in adult females (Fig 3) assumes a lack of adjustment downward for age in males and an adjustment upward for iron deficiency in females. Although mean Hb level representing the fifth percentile decreases among males older than 60 years, it is clear that a substantial fraction of older males with low Hb levels show concurrent evidence of pathological conditions that may cause or contribute to anemia.[32] Because we cannot exclude potential pathological states, we cannot assume that lower Hb levels in older males are normal. Therefore, we make no adjustment for age among males. The recommended threshold of less than 12.0 g/dL in females reflects exclusion from the healthy population of individuals whose iron status test results suggest that iron deficiency is contributing to a low Hb level.

The recommended definition of anemia differs from previous CPGs. The WHO defines anemia as a Hb level less than 13.0 g/dL in adult men and less than 12 g/dL in adult women.[42] Differences between the current recommendation and the WHO definition arise from differences in the data source for the general population: the WHO definition is based on sparse data obtained prior to 1968, whereas the definition proposed in the current guidelines is based on more recent NHANES III data. The recently published Revised EBPG for the Management of Anaemia in Patients with Chronic Renal Failure also defines anemia as a Hb level less than 13 g/dL in men, but adjust this to less than 12 g/dL for men older

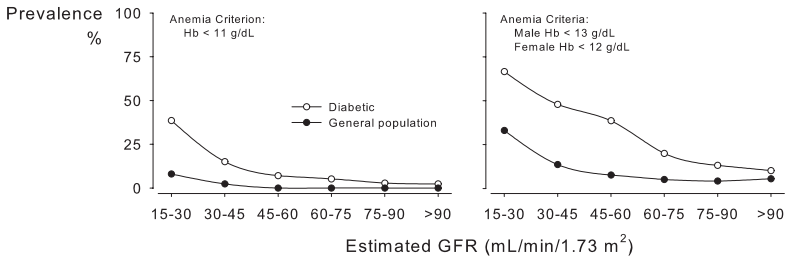


**Fig 9. Prevalence of low Hb level by eGFR in patients with diabetes compared with the general population. Open circles (○) indicate the diabetic population, while closed circles (●) represent general population data from NHANES III. A: Hb ≤11 g/dL; B: WHO criteria (men, Hb <13 g/dL; women, Hb <12 g/dL). Reprinted with permission.[35]**

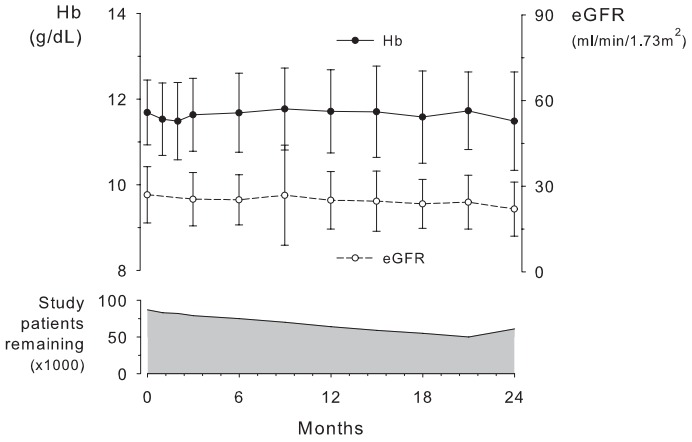


**Fig 10. Changes in Hb levels and eGFR over 2 years in adult patients with CKD stages 3 and 4 not treated with ESA. Oral iron supplements and occasional IV iron treatment were administered to maintain TSAT at greater than 20% and ferritin levels greater than 100 ng/mL. Data given as mean ± SD. Although mean Hb levels showed little or no change, the number of study patients remaining without ESA therapy declined. Results courtesy of the authors, from control group patients previously described. Reprinted with permission.[39]**

**Table 7. Hb for Males by Race/Ethnicity and Age: United States, 1988 to 1994**

| Race/ethnicity and age | Number of examined persons | Mean | Standard deviation | Standard error of mean | Percentile | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 2.5th | 5th | 10th | 15th | 25th | 50th | 75th | 85th | 90th | 95th | 97.5th |
| All race/ethnic groups[1] | | | | | | | | | | | | | | | |
| 1 year and over | 12,623 | 146.7 | 13.9 | 0.347 | 116.6 | 121.0 | 126.6 | 131.6 | 138.7 | 148.6 | 156.5 | 160.5 | 163.1 | 167.1 | 170.2 |
| 1–2 years | 931 | 120.1 | 8.2 | 0.448 | 104.6 | 107.0 | 109.1 | 112.1 | 115.0 | 120.0 | 125.6 | 128.2 | 130.6 | 133.2 | 136.1 |
| 3–5 years | 1,281 | 123.5 | 7.7 | 0.362 | 108.5 | 111.5 | 114.5 | 116.1 | 118.6 | 123.0 | 128.2 | 132.2 | 134.2 | 136.7 | 139.0 |
| 6–8 years | 709 | 128.8 | 8.0 | 0.505 | 113.6 | 115.1 | 119.0 | 120.6 | 124.1 | 129.1 | 134.1 | 137.1 | 138.7 | 141.7 | 145.1 |
| 9–11 years | 773 | 132.8 | 8.4 | 0.505 | 117.1 | 119.6 | 122.5 | 124.5 | 127.5 | 133.5 | 139.2 | 141.6 | 144.0 | 146.0 | 148.2 |
| 12–14 years | 540 | 141.4 | 10.8 | 0.778 | 120.5 | 124.1 | 127.1 | 130.7 | 133.7 | 142.1 | 149.2 | 153.1 | 154.6 | 159.0 | 163.0 |
| 15–19 years | 836 | 150.7 | 10.3 | 0.599 | 130.6 | 134.6 | 137.6 | 140.0 | 144.2 | 151.1 | 157.6 | 160.6 | 163.5 | 168.7 | 170.7 |
| 20–29 years | 1,562 | 154.1 | 9.2 | 0.390 | 137.1 | 139.5 | 142.7 | 144.7 | 147.6 | 154.6 | 160.6 | 163.2 | 165.2 | 168.6 | 172.1 |
| 30–39 years | 1,401 | 152.5 | 10.2 | 0.457 | 133.1 | 136.1 | 140.1 | 142.2 | 146.1 | 152.7 | 159.7 | 163.2 | 165.1 | 168.7 | 171.6 |
| 40–49 years | 1,164 | 151.2 | 10.2 | 0.499 | 129.7 | 134.6 | 138.7 | 142.0 | 145.5 | 151.7 | 157.7 | 160.7 | 164.0 | 168.0 | 171.0 |
| 50–59 years | 833 | 150.3 | 11.2 | 0.652 | 126.1 | 132.0 | 136.7 | 140.0 | 143.5 | 151.1 | 157.6 | 161.6 | 163.5 | 168.6 | 172.1 |
| 60–69 years | 1,130 | 147.6 | 11.5 | 0.574 | 123.6 | 128.2 | 133.7 | 136.6 | 141.1 | 147.7 | 154.5 | 158.6 | 161.7 | 166.7 | 170.1 |
| 70 years and over | 1,463 | 143.6 | 14.3 | 0.627 | 110.5 | 116.6 | 125.6 | 130.6 | 136.1 | 144.7 | 153.1 | 156.6 | 160.1 | 164.7 | 168.5 |
| Non-Hispanic white | | | | | | | | | | | | | | | |
| 1 year and over | 4,491 | 147.8 | 13.3 | 0.398 | 118.1 | 123.0 | 129.0 | 133.7 | 140.6 | 149.6 | 157.1 | 160.7 | 163.2 | 167.2 | 170.6 |
| 1–2 years | 297 | 120.4 | 7.6 | 0.528 | * | 108.1 | 111.1 | 113.0 | 115.1 | 120.0 | 125.6 | 128.2 | 130.2 | 133.2 | * |
| 3–5 years | 323 | 124.1 | 7.5 | 0.497 | * | 113.1 | 115.0 | 116.6 | 119.1 | 123.1 | 128.7 | 133.1 | 134.7 | 137.7 | * |
| 6–8 years | 190 | 129.8 | 7.6 | 0.662 | * | * | 120.6 | 123.0 | 125.6 | 130.0 | 135.0 | 137.2 | 139.6 | * | * |
| 9–11 years | 200 | 134.1 | 7.6 | 0.641 | * | * | 124.1 | 126.1 | 128.2 | 134.1 | 140.2 | 142.1 | 144.2 | * | * |
| 12–14 years | 139 | 142.3 | 10.2 | 1.040 | * | * | 129.1 | 132.0 | 134.6 | 142.6 | 150.2 | 153.2 | 154.7 | * | * |
| 15–19 years | 195 | 151.6 | 9.3 | 0.802 | * | * | 139.2 | 141.0 | 146.2 | 152.0 | 158.1 | 160.6 | 162.5 | * | * |
| 20–29 years | 381 | 154.9 | 8.8 | 0.538 | * | 141.6 | 143.6 | 145.6 | 148.5 | 155.5 | 161.1 | 163.7 | 165.7 | 168.6 | * |
| 30–39 years | 435 | 153.0 | 9.7 | 0.556 | * | 137.7 | 141.0 | 143.2 | 146.7 | 153.0 | 160.0 | 163.2 | 165.1 | 168.7 | * |
| 40–49 years | 414 | 152.1 | 9.7 | 0.573 | * | 137.0 | 140.2 | 142.7 | 146.2 | 152.6 | 158.2 | 161.2 | 164.2 | 168.2 | * |
| 50–59 years | 410 | 151.1 | 10.9 | 0.648 | * | 133.1 | 138.5 | 140.7 | 144.0 | 152.0 | 158.0 | 161.7 | 164.0 | 169.7 | * |
| 60–69 years | 493 | 148.2 | 11.2 | 0.603 | * | 128.7 | 134.6 | 137.2 | 141.7 | 148.5 | 154.7 | 159.6 | 162.5 | 167.1 | * |
| 70 years and over | 1,014 | 144.5 | 13.7 | 0.516 | * | 119.6 | 127.6 | 132.2 | 137.1 | 146.1 | 153.2 | 157.0 | 160.2 | 165.1 | * |
| Non-Hispanic black | | | | | | | | | | | | | | | |
| 1 year and over | 3,633 | 139.4 | 14.6 | 0.339 | 110.1 | 115.1 | 119.6 | 123.0 | 129.2 | 141.1 | 150.0 | 154.1 | 157.0 | 161.6 | 164.5 |
| 1–2 years | 275 | 117.2 | 8.3 | 0.568 | * | 103.1 | 106.6 | 108.0 | 112.5 | 117.6 | 123.0 | 125.6 | 127.0 | 130.7 | * |
| 3–5 years | 419 | 120.1 | 8.2 | 0.457 | * | 105.6 | 109.0 | 112.5 | 116.0 | 120.5 | 125.6 | 128.0 | 130.2 | 134.6 | * |
| 6–8 years | 229 | 125.3 | 8.6 | 0.645 | * | 112.1 | 115.1 | 117.1 | 120.1 | 125.1 | 130.5 | 134.2 | 136.2 | 138.7 | * |
| 9–11 years | 267 | 126.7 | 9.5 | 0.665 | * | 114.6 | 117.1 | 119.0 | 122.1 | 126.6 | 132.2 | 136.1 | 137.6 | 140.0 | * |
| 12–14 years | 184 | 133.1 | 10.9 | 0.916 | * | * | 120.1 | 123.0 | 126.5 | 132.7 | 140.5 | 144.5 | 145.6 | * | * |
| 15–19 years | 298 | 145.3 | 10.1 | 0.666 | * | 128.6 | 132.5 | 135.1 | 138.7 | 145.7 | 152.1 | 155.2 | 158.2 | 160.7 | * |
| 20–29 years | 463 | 148.5 | 9.4 | 0.498 | * | 134.0 | 137.2 | 139.2 | 142.2 | 148.2 | 154.5 | 158.7 | 161.7 | 164.6 | * |
| 30–39 years | 461 | 145.7 | 11.9 | 0.632 | * | 127.1 | 132.6 | 135.6 | 140.1 | 145.7 | 153.2 | 156.6 | 159.2 | 163.1 | * |
| 40–49 years | 336 | 145.0 | 10.9 | 0.681 | * | 127.0 | 130.6 | 134.0 | 138.5 | 145.2 | 152.2 | 157.0 | 158.6 | 162.1 | * |
| 50–59 years | 207 | 143.1 | 13.0 | 1.034 | * | * | 124.6 | 129.6 | 135.6 | 143.6 | 151.7 | 157.1 | 160.1 | * | * |
| 60–69 years | 274 | 139.0 | 13.7 | 0.944 | * | 114.0 | 121.5 | 126.5 | 132.7 | 140.0 | 148.2 | 152.7 | 154.6 | 159.6 | * |
| 70 years and over | 220 | 134.3 | 15.0 | 1.153 | * | * | 115.6 | 120.6 | 127.0 | 136.1 | 143.6 | 147.7 | 152.6 | * | * |
| Mexican American | | | | | | | | | | | | | | | |
| 1 year and over | 3,951 | 146.8 | 14.7 | 0.604 | 115.6 | 120.1 | 125.1 | 129.2 | 137.2 | 149.2 | 157.7 | 161.6 | 163.7 | 167.1 | 170.1 |
| 1–2 years | 298 | 120.1 | 9.4 | 0.859 | * | * | 108.6 | 110.5 | 115.0 | 121.1 | 126.1 | 129.2 | 131.6 | * | * |
| 3–5 years | 466 | 124.8 | 7.7 | 0.560 | * | 112.5 | 115.5 | 117.1 | 120.1 | 125.1 | 129.6 | 133.1 | 134.7 | 137.6 | * |
| 6–8 years | 250 | 129.4 | 8.3 | 0.827 | * | * | 119.6 | 122.0 | 124.0 | 129.1 | 134.2 | 137.0 | 140.2 | * | * |
| 9–11 years | 272 | 133.9 | 8.5 | 0.815 | * | * | 122.5 | 124.5 | 127.5 | 134.7 | 140.6 | 142.6 | 144.2 | * | * |
| 12–14 years | 191 | 140.8 | 9.0 | 1.028 | * | * | 130.7 | 132.0 | 134.1 | 140.2 | 146.7 | 149.7 | 152.1 | * | * |
| 15–19 years | 304 | 153.0 | 9.2 | 0.834 | * | 139.0 | 141.2 | 144.0 | 146.2 | 153.1 | 160.1 | 163.2 | 164.7 | 167.1 | * |
| 20–29 years | 647 | 155.3 | 8.9 | 0.551 | * | 140.5 | 143.5 | 146.2 | 149.6 | 155.7 | 161.6 | 164.2 | 166.6 | 169.7 | * |
| 30–39 years | 450 | 154.4 | 8.6 | 0.639 | * | 141.0 | 143.0 | 145.5 | 148.7 | 154.6 | 160.7 | 163.7 | 165.2 | 167.7 | * |
| 40–49 years | 369 | 152.6 | 10.6 | 0.872 | * | 136.2 | 139.7 | 142.6 | 146.1 | 153.7 | 159.1 | 163.2 | 165.5 | 168.7 | * |
| 50–59 years | 175 | 150.8 | 11.6 | 1.381 | * | * | 137.2 | 140.1 | 144.7 | 151.2 | 159.5 | 162.6 | 164.1 | * | * |
| 60–69 years | 330 | 148.8 | 11.8 | 1.019 | * | 129.2 | 135.2 | 137.7 | 141.7 | 149.2 | 156.1 | 161.0 | 162.7 | 165.2 | * |
| 70 years and over | 199 | 143.9 | 15.2 | 1.697 | * | * | 125.5 | 126.1 | 135.0 | 146.2 | 156.2 | 160.5 | 162.0 | * | * |

* Does not meet standards for reliability or precision.
[1]Includes all other race/ethnic groups not listed separately.

Data represent Hb in mg/L for males 1 year and over, number of examined persons, mean, standard deviation, standard error of the mean, and selected percentile, by race/ethnicity and age in the US, from 1988 through 1994.
Reprinted with permission.[40]

than 70 years. Because the EBPGs do not adjust for the potential contribution of iron deficiency in women, the EBPG threshold for women is less than 11.5 g/dL.[16] Finally, the previous KDOQI Anemia Guidelines recommended less than 12 g/dL for men (reflecting use of a different data set), less than 11 g/dL for women of reproductive age (different data set, no attempt to exclude effect of iron deficiency), and less than 12 g/dL for postmenopausal women (no change).

The importance of identifying patients with anemia in the presence of CKD is 2-fold. First, a Hb value in the lowest fifth percentile of the general population may signify the presence of significant nutritional deficits, systemic illness, or other disorders that warrant attention. Second, anemia in patients with CKD is a known risk

**Table 8. Hb for Females by Race/Ethnicity and Age: United States, 1988 to 1994**

| Race/ethnicity and age | Number of examined persons | Mean | Standard deviation | Standard error of mean | Percentile | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 2.5th | 5th | 10th | 15th | 25th | 50th | 75th | 85th | 90th | 95th | 97.5th |
| All race/ethnic groups[1] | | | | | | | | | | | | | | | |
| 1 year and over | 13,749 | 131.9 | 11.0 | 0.263 | 110.1 | 114.0 | 118.5 | 121.1 | 125.5 | 132.2 | 139.1 | 143.1 | 145.6 | 149.2 | 152.7 |
| 1–2 years | 858 | 120.2 | 8.0 | 0.507 | 105.1 | 108.0 | 110.1 | 112.5 | 115.1 | 120.1 | 125.5 | 129.0 | 130.6 | 133.2 | 137.0 |
| 3–5 years | 1,337 | 123.9 | 7.7 | 0.393 | 108.6 | 111.1 | 114.1 | 116.1 | 119.0 | 124.0 | 129.2 | 132.2 | 133.7 | 136.2 | 137.7 |
| 6–8 years | 675 | 128.2 | 7.7 | 0.549 | 112.5 | 115.0 | 118.0 | 119.1 | 123.1 | 129.5 | 133.6 | 135.7 | 137.6 | 140.1 | 143.2 |
| 9–11 years | 734 | 131.0 | 7.8 | 0.536 | 117.0 | 118.5 | 121.5 | 122.6 | 126.6 | 130.6 | 136.2 | 139.2 | 140.6 | 144.2 | 146.6 |
| 12–14 years | 621 | 132.9 | 10.0 | 0.743 | 113.1 | 117.0 | 120.5 | 123.1 | 126.1 | 132.6 | 140.5 | 143.7 | 146.5 | 149.2 | 151.2 |
| 15–19 years | 950 | 131.5 | 10.0 | 0.603 | 112.0 | 114.6 | 119.0 | 121.6 | 125.1 | 132.1 | 138.7 | 142.2 | 144.2 | 146.6 | 148.7 |
| 20–29 years | 1,769 | 131.4 | 10.6 | 0.468 | 109.6 | 113.6 | 118.5 | 120.6 | 124.6 | 132.1 | 138.7 | 142.0 | 144.7 | 147.6 | 150.0 |
| 30–39 years | 1,757 | 132.2 | 11.3 | 0.500 | 108.5 | 113.0 | 117.6 | 121.1 | 126.1 | 133.0 | 139.6 | 142.7 | 146.2 | 150.2 | 152.7 |
| 40–49 years | 1,303 | 132.2 | 11.8 | 0.607 | 104.5 | 112.0 | 119.0 | 122.6 | 127.0 | 132.7 | 139.6 | 143.5 | 145.6 | 149.5 | 152.5 |
| 50–59 years | 969 | 135.1 | 10.6 | 0.636 | 114.6 | 117.5 | 122.5 | 125.5 | 129.0 | 134.6 | 142.2 | 146.6 | 148.7 | 152.7 | 155.1 |
| 60–69 years | 1,112 | 134.8 | 11.1 | 0.619 | 113.1 | 116.5 | 121.1 | 124.0 | 128.1 | 135.6 | 141.7 | 145.7 | 147.7 | 152.0 | 154.6 |
| 70 years and over | 1,664 | 133.7 | 11.8 | 0.536 | 108.5 | 113.6 | 119.5 | 122.6 | 127.1 | 134.2 | 141.6 | 145.2 | 147.6 | 152.1 | 156.2 |
| Non-Hispanic white | | | | | | | | | | | | | | | |
| 1 year and over | 5,030 | 133.5 | 10.4 | 0.294 | 112.6 | 116.5 | 120.6 | 123.1 | 127.1 | 133.6 | 140.2 | 144.1 | 146.6 | 150.2 | 153.6 |
| 1–2 years | 270 | 120.5 | 7.3 | 0.593 | * | 108.5 | 111.5 | 113.5 | 116.1 | 120.1 | 125.0 | 128.7 | 130.2 | 132.5 | * |
| 3–5 years | 332 | 124.8 | 7.0 | 0.514 | * | 113.6 | 116.1 | 118.1 | 120.0 | 124.5 | 130.0 | 132.2 | 134.2 | 137.0 | * |
| 6–8 years | 175 | 129.2 | 7.2 | 0.725 | * | * | 119.1 | 120.6 | 125.5 | 129.7 | 133.7 | 135.7 | 137.5 | * | * |
| 9–11 years | 186 | 132.2 | 7.8 | 0.757 | * | * | 122.0 | 125.0 | 127.6 | 132.1 | 137.2 | 140.1 | 142.0 | * | * |
| 12–14 years | 154 | 134.3 | 9.7 | 1.043 | * | * | 122.1 | 124.6 | 127.6 | 133.1 | 141.7 | 144.6 | 148.6 | * | * |
| 15–19 years | 270 | 133.3 | 9.2 | 0.742 | * | 117.6 | 121.6 | 123.5 | 127.5 | 133.2 | 140.0 | 143.2 | 145.0 | 147.5 | * |
| 20–29 years | 477 | 133.0 | 10.0 | 0.610 | * | 115.6 | 120.1 | 122.6 | 126.5 | 134.1 | 140.1 | 143.6 | 145.2 | 148.1 | * |
| 30–39 years | 572 | 134.2 | 10.2 | 0.565 | * | 116.5 | 122.0 | 125.0 | 128.0 | 134.5 | 140.7 | 144.5 | 147.6 | 151.7 | * |
| 40–49 years | 457 | 133.9 | 10.3 | 0.643 | * | 117.6 | 122.6 | 124.6 | 128.2 | 133.7 | 140.6 | 144.2 | 146.7 | 149.7 | * |
| 50–59 years | 473 | 136.1 | 10.2 | 0.627 | * | 120.5 | 124.0 | 126.6 | 129.7 | 135.7 | 143.5 | 147.2 | 150.0 | 153.7 | * |
| 60–69 years | 473 | 135.3 | 10.9 | 0.665 | * | 116.6 | 121.6 | 125.1 | 128.6 | 136.1 | 142.5 | 146.1 | 148.2 | 152.1 | * |
| 70 years and over | 1,191 | 134.4 | 11.1 | 0.429 | * | 115.5 | 121.0 | 123.6 | 127.6 | 134.7 | 141.7 | 145.5 | 147.7 | 153.0 | * |
| Non-Hispanic black | | | | | | | | | | | | | | | |
| 1 year and over | 4,116 | 124.6 | 11.4 | 0.247 | 99.1 | 107.1 | 111.5 | 114.1 | 118.1 | 125.1 | 131.7 | 135.6 | 138.1 | 142.6 | 145.7 |
| 1–2 years | 265 | 118.3 | 8.5 | 0.628 | * | 104.5 | 107.6 | 110.0 | 112.5 | 119.0 | 124.0 | 127.0 | 129.0 | 132.6 | * |
| 3–5 years | 433 | 120.7 | 7.8 | 0.448 | * | 109.0 | 111.5 | 113.1 | 115.6 | 120.6 | 126.0 | 128.2 | 130.6 | 133.2 | * |
| 6–8 years | 220 | 123.7 | 7.7 | 0.620 | * | * | 113.5 | 115.1 | 118.1 | 123.6 | 129.5 | 131.7 | 134.5 | * | * |
| 9–11 years | 252 | 126.5 | 7.8 | 0.592 | * | 115.1 | 117.1 | 118.5 | 121.6 | 126.5 | 131.1 | 134.7 | 137.2 | 140.6 | * |
| 12–14 years | 220 | 125.4 | 8.9 | 0.717 | * | * | 113.1 | 116.0 | 119.6 | 125.5 | 132.6 | 134.7 | 136.2 | * | * |
| 15–19 years | 326 | 123.2 | 10.0 | 0.666 | * | 106.6 | 112.1 | 114.1 | 118.0 | 123.6 | 129.1 | 133.1 | 136.1 | 139.5 | * |
| 20–29 years | 589 | 124.2 | 11.0 | 0.546 | * | 107.0 | 111.1 | 113.6 | 118.1 | 124.1 | 131.6 | 135.2 | 138.0 | 142.0 | * |
| 30–39 years | 602 | 124.4 | 12.2 | 0.596 | * | 103.5 | 110.1 | 113.1 | 117.5 | 125.1 | 132.2 | 136.1 | 138.2 | 143.1 | * |
| 40–49 years | 425 | 124.2 | 13.8 | 0.802 | * | 101.1 | 109.0 | 111.6 | 118.0 | 126.0 | 132.6 | 136.2 | 138.1 | 142.6 | * |
| 50–59 years | 256 | 129.0 | 11.3 | 0.845 | * | 110.6 | 116.1 | 118.6 | 123.6 | 129.2 | 135.6 | 140.2 | 142.6 | 145.7 | * |
| 60–69 years | 276 | 128.6 | 10.6 | 0.767 | * | 112.1 | 115.6 | 118.1 | 121.6 | 129.2 | 135.6 | 140.1 | 142.2 | 146.1 | * |
| 70 years and over | 252 | 124.6 | 14.0 | 1.057 | * | 97.5 | 108.0 | 111.0 | 116.6 | 126.1 | 132.7 | 138.2 | 143.0 | 146.7 | * |
| Mexican American | | | | | | | | | | | | | | | |
| 1 year and over | 3,994 | 130.2 | 11.3 | 0.464 | 106.0 | 112.0 | 117.0 | 119.6 | 123.6 | 130.7 | 137.6 | 141.1 | 143.2 | 147.5 | 150.5 |
| 1–2 years | 285 | 120.7 | 8.9 | 0.820 | * | * | 111.5 | 113.1 | 115.6 | 121.0 | 126.6 | 129.6 | 131.2 | * | * |
| 3–5 years | 506 | 124.5 | 8.0 | 0.556 | * | 111.1 | 115.5 | 116.6 | 119.0 | 124.6 | 130.1 | 133.0 | 135.1 | 137.5 | * |
| 6–8 years | 257 | 128.8 | 7.8 | 0.755 | * | * | 119.6 | 122.0 | 123.5 | 128.6 | 135.2 | 137.6 | 137.7 | * | * |
| 9–11 years | 265 | 131.8 | 7.6 | 0.726 | * | * | 123.0 | 123.1 | 126.6 | 131.1 | 136.5 | 139.2 | 141.5 | * | * |
| 12–14 years | 218 | 133.2 | 8.5 | 0.897 | * | * | 121.1 | 124.5 | 126.6 | 133.5 | 138.7 | 142.7 | 143.6 | * | * |
| 15–19 years | 297 | 129.9 | 10.8 | 0.973 | * | 114.0 | 116.6 | 119.1 | 123.6 | 130.7 | 137.2 | 140.2 | 142.1 | 145.2 | * |
| 20–29 years | 632 | 130.4 | 10.6 | 0.655 | * | 112.1 | 116.6 | 119.6 | 124.0 | 131.5 | 137.7 | 140.2 | 142.6 | 146.2 | * |
| 30–39 years | 504 | 129.9 | 11.7 | 0.814 | * | 108.5 | 117.1 | 120.0 | 123.6 | 131.1 | 138.1 | 140.7 | 142.7 | 145.7 | * |
| 40–49 years | 356 | 130.1 | 15.3 | 1.257 | * | 99.6 | 111.1 | 116.6 | 124.1 | 132.2 | 139.2 | 143.5 | 146.7 | 151.1 | * |
| 50–59 years | 185 | 135.5 | 11.5 | 1.311 | * | * | 122.0 | 125.6 | 129.7 | 136.1 | 143.6 | 147.0 | 149.1 | * | * |
| 60–69 years | 317 | 134.2 | 11.2 | 0.978 | * | 117.1 | 120.6 | 123.0 | 127.1 | 134.1 | 142.6 | 145.6 | 147.5 | 150.2 | * |
| 70 years and over | 172 | 134.1 | 14.0 | 1.655 | * | * | 119.1 | 122.6 | 126.6 | 136.1 | 143.7 | 146.2 | 149.1 | * | * |

* Does not meet standards for reliability or precision.
[1]Includes all other race/ethnic groups not listed separately.

Data represent Hb in mg/L for females 1 year and over, number of examined persons, mean, standard deviation, standard error of the mean, and selected percentile, by race/ethnicity and age in the US, from 1988 through 1994.
Reprinted with permission.[40]

factor for a number of significant adverse patient outcomes, including hospitalizations, CVD, cognitive impairment, and mortality.[16,43-50] Regardless of whether concurrent disorders, if any, are treatable, awareness of their presence is likely to be helpful to the clinician. Similarly, the benefits of anemia treatment (see Guideline 2.1) cannot extend to patients whose anemia remains unidentified.

Altitude, age, race, and smoking each contribute to the interpretation of the normal range of Hb values, in addition to sex, and therefore must be considered in patients with CKD. The current definition for anemia reflects results from adult patients older than 18 years, of all races and ethnic groups, and living at relatively low altitude (<1,000 m or 3,000 ft).

Altitude has a direct impact on red blood cell number, mass, and volume.[51] Generally, Hb concentration can be expected to increase by about 0.6 g/dL in women and 0.9 g/dL in men for each 1,000 m of altitude above sea level.[52] This in-

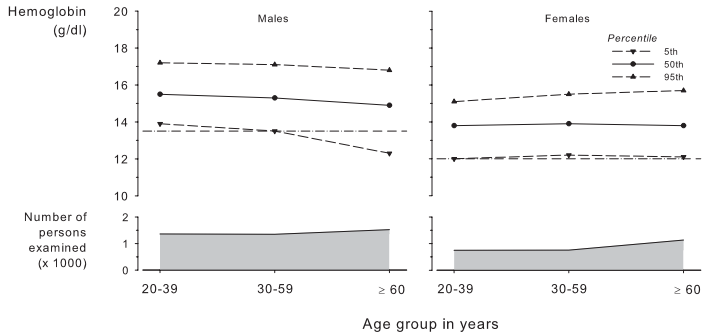


**Fig 11. Distribution of Hb levels in adult males and females by age group. The 5th, 50th, and 95th percentiles are shown for each age group. In females, results reflect only individuals with serum ferritin greater than 25 ng/mL or TSAT greater than 16% because lower values may contribute to low Hb levels. Dash-dot-dash lines indicate recommended cutoff value to define anemia. (Source: US Renal Data System [USRDS] special data request, NHANES 1999-2002 data set).**

crease in Hb levels seems to be caused at least in part by increased erythropoietin production.[53] The threshold Hb level defining anemia in patients living at high altitude should be adjusted upward, in keeping with the degree of elevation (Table 9).

In children, mean Hb level and the variability around the mean vary highly with age. These findings are discussed elsewhere in more detail (in CPR for Children 1.1). Among adult males, as previously noted, the lower fifth percentile of Hb values declines as age advances (Fig 11). One study reported a mean decrease of 1 to 1.5 g/dL in Hb concentration in males as they increased in age from 50 to 75 years; however, this trend was not seen in women, in whom Hb concentration remained stable between 20 and 80 years of age.[54] Although it previously was believed that decreases in Hb levels might be a consequence of normal aging, evidence has accumulated that anemia reflects poor health and increased vulnerability to adverse outcomes in older persons.[32] Consequently, the current recommendation makes no adjustment for aging in men. An association between an increasing prevalence of anemia and older age has been reported in most,[27,55] but not all,[29] studies of patients with CKD, in keeping with current opinion that anemia is not a normal consequence of aging.[56]

Among women of reproductive age, menstrual losses, the potential for iron deficiency, and the effect of pregnancy each deserve consideration. Although Hb values in women are lower than those in men (Table 7 and 8), Hb concentrations in iron-replete women remain stable between 20 and 80 years of age.[54] Regardless of the presence or absence of CKD, the prevalence of anemia is greater in women compared with men.[55] Menses and pregnancy may each contribute to this finding. Menstrual losses of iron average 0.3 to 0.5 mg/d and may result in mostly iron-deficiency anemia.[42] Among pregnant women, Hb concentration decreases during the first and second trimesters largely because of the dilutional effect of expanding blood volume. In the third trimester, Hb concentration remains low in pregnant women who do not take iron supplements, but gradually increases toward prepregnancy levels in those who take iron supplements.[57-59] Table 10 shows maximum Hb cutoff values for anemia during pregnancy.

Hb values also vary significantly between races, with African-American individuals consistently showing Hb concentrations 0.5- to 0.9-

**Table 9. Normal Increase in Hb Levels Related to Long-Term Altitude Exposure**

| Altitude (meters) | Increase in Hb (g/dL) |
|---|---|
| <1,000 | 0 |
| 1,000 | +0.2 |
| 1,500 | +0.5 |
| 2,000 | +0.8 |
| 2,500 | +1.3 |
| 3,000 | +1.9 |
| 3,500 | +2.7 |
| 4,000 | +3.5 |
| 4,500 | +4.5 |

Reprinted with permission.[42]

**Table 10. Maximum Hb Cutoff Values for Anemia in Pregnancy**

| Weeks' Gestation | Hb Concentration (g/dL) |
|---|---|
| 12 | 11.0 |
| 16 | 10.6 |
| 20 | 10.5 |
| 24 | 10.5 |
| 28 | 10.7 |
| 32 | 11.0 |
| 36 | 11.4 |
| 40 | 11.9 |
| Trimester | |
| First | 11.0 |
| Second | 10.5 |
| Third | 11.0 |

Maximum cutoff values for anemia are based on the 5th percentile from the third National Health and Nutrition Examination Survey (NHANES III), which excluded persons who had a high likelihood of iron deficiency. Maximum values for anemia during pregnancy are based on values from pregnant women who had adequate supplementation.
Reprinted with permission.[41]

g/dL lower than those of Caucasoid or Oriental populations.[60-62] Because the reason for this disparity in Hb level distributions by race has not been determined and could reflect increased disease burden, this guideline does not provide race-specific cutoff values for anemia.[41,63,64] Anemia may develop at an earlier stage in the course of CKD among non-Hispanic African Americans compared with individuals of other races.[27] African-American patients have a greater prevalence of anemia at every stage of CKD compared with whites.[55]

Last, smoking is associated with elevated carboxyhemoglobin levels, which are associated with a compensatory increase in total Hb concentration.[65] If the same definition of anemia is applied to both smokers and nonsmokers, the risk for developing anemia is lower in current or past smokers than nonsmokers.[55] Because approximately 20% to 40% of patients with CKD are current or past smokers,[55] consideration should be given to the significance of a smoking history in interpreting results of Hb measurement (Table 11).

## LIMITATIONS

Many studies that examined the relationship between Hb level and kidney function:

1. Have been cross-sectional and not longitudinal in design.
2. Described patients entered into clinical trials or seen by nephrologists, which are not a truly representative sample of patients with CKD.
3. Included small numbers of patients with lower levels of kidney function.
4. Used a great variety of methods to assess level of kidney function. It therefore is difficult to determine whether the variability in Hb at levels of kidney function is caused by variability in measurements of kidney function or variability associated with CKD itself.
5. Used the MDRD4 formula to estimate GFR, the precision of which decreases at higher levels of kidney function.
6. Did not describe the cause of the anemia in patients with CKD.

**Table 11. Adjustment to Hb for Smoking by Number of Packets per Day**

| Group | Hb (g/dL) |
|---|---|
| Nonsmokers | 0 |
| Smokers (all) | +0.3 |
| 0.5-1 packet/day | +0.3 |
| 1-2 packets/day | +0.5 |
| >2 packets/day | +0.7 |

Reprinted with permission.[55]

# CPR 1.2.: EVALUATION OF ANEMIA IN CKD

Anemia in patients with CKD is not always caused by erythropoietin deficiency alone. Initial laboratory evaluation therefore is aimed at identifying other factors that may cause or contribute to anemia or lead to ESA hyporesponsiveness.

**1.2.1 In the opinion of the Work Group, initial assessment of anemia should include the following tests:**

**1.2.1.1 A complete blood count (CBC) including—in addition to the Hb concentration—red blood cell indices (mean corpuscular hemoglobin [MCH], mean corpuscular volume [MCV], mean corpuscular hemoglobin concentration [MCHC]), white blood cell count, and differential and platelet count.**

**1.2.1.2 Absolute reticulocyte count.**

**1.2.1.3 Serum ferritin to assess iron stores.**

**1.2.1.4 Serum TSAT *or* content of Hb in reticulocytes (CHr) to assess adequacy of iron for erythropoiesis.**

## BACKGROUND

Although erythropoietin deficiency is common among patients with anemia and CKD, other potential causes and potentially contributing disorders should be identified or excluded. The recommended laboratory evaluation provides information regarding the degree and cause of anemia, activity of the erythroid and nonerythroid marrow, and assessment of iron stores and iron availability for erythropoiesis. In particular, clinicians should consider causes of anemia other than erythropoietin deficiency when: (1) severity of the anemia is disproportionate to the deficit in renal function; (2) there is evidence of iron deficiency, or (3) there is evidence of leukopenia or thrombocytopenia. An evaluation of the cause of anemia should precede initiation of ESA therapy. This guideline provides a framework for understanding the tests used in the initial evaluation of anemia and sheds light on the utility of test results in evaluating iron status.

## RATIONALE

### *Initial Assessment of Anemia*

The CBC provides information about the severity of anemia, adequacy of nutrients (including folate, vitamin $B_{12}$, and iron), and adequacy of bone marrow function.

Severity of anemia is assessed best by measuring Hb concentration rather than Hct because Hb is a stable analyte that is measured directly. The Hb assay is standardized and is not influenced by differences in instrumentation. Conversely, Hct measurement is relatively unstable and lacks standardization. The Hct result is derived indirectly by automated analyzers and is instrumentation dependent.[16] Analytical advantages of Hb level over Hct are described next.[2]

Although blood-sample storage conditions have no effect on Hb measurement, Hct increases with storage temperature and duration because stored red blood cells swell. The MCV from which the Hct is calculated (MCV $\times$ erythrocyte count) increases after 8 hours of storage at room temperature and after 24 hours when refrigerated.[86] The degree of MCV increase after sample storage may erroneously elevate the resulting Hct value by as much as 2 to 4 Hct percentage points.[87] Long sample shipping distances and sample transit times, as commonly required for US dialysis facilities, increase the risk for introducing error into Hct results.

Hyperglycemia is associated with an increase in MCV (but not Hb level) and therefore spuriously elevates the Hct result.[88,89]

The coefficient of variation for same-sample Hct is greater than that for Hb, largely because of variability in the number and size of erythrocytes counted to calculate the Hct.[90] Within-run and between-run coefficients of variation in automated analyzer measurements of Hb are one half and one third those for Hct, respectively.[91]

For these reasons, Hct is an unacceptable test to evaluate anemia, and Hb should be the standard measure for assessing anemia.

Hb should be measured on standardized automated blood count analyzers in an accredited laboratory. In patients with non–dialysis-dependent (ND) CKD (ND-CKD) and patients with PD-dependent CKD (PD-CKD), the timing of the blood sample draw is not critical because

plasma volume in these patients remains relatively constant. However, in patients with HD-dependent CKD (HD-CKD), interdialytic weight gain contributes to a dilutional decrease in Hb level, whereas intradialytic ultrafiltration promotes a contractional increase in Hb level. Thus, a sample obtained immediately before dialysis and during volume expansion underestimates the euvolemic Hb level, whereas a sample obtained immediately after dialysis overestimates the euvolemic Hb. In a study of 68 stable HD patients, mean predialysis versus postdialysis Hb levels were 10.5 ± 1.3 and 11.5 ± 1.3 g/dL, respectively.[92] There was a strong linear inverse correlation between percentage of change in Hb and Hct values and percentage of change in body weight, indicating that increments in Hb and Hct values after dialysis were a direct function of the intradialytic variation in body weight and degree of ultrafiltration. Moreover, the predialysis Hb level measured after a long interdialytic period (3 days) was 0.5 to 0.6 g/dL less than the predialysis Hb level measured after a short interdialytic period (2 days). Among all pre-HD and post-HD Hb values, levels measured at the end of short intervals were closest to the mean Hb value of the week, derived from calculation of the area under the curve.[93]

Given the relationship between Hb level and interdialytic weight gain in patients with HD-CKD, midweek predialysis sampling theoretically is optimal. However, information that patient outcomes are affected by sampling day in patients with HD-CKD is lacking. Moreover, logistical considerations preclude sampling all patients with HD-CKD at midweek. Therefore, sampling for Hb determination should be performed before dialysis without specific reference to dialysis day. In the interpretation of results, consideration should be given to the potential effect of the patient's volume status.

In addition to Hb, other reported results of the CBC may convey important clinical information. Deficiency of folate or vitamin $B_{12}$ may lead to macrocytosis, whereas iron deficiency or inherited disorders of Hb formation ($\alpha$- or $\beta$-thalassemia) may produce microcytosis. Macrocytosis with leukopenia or thrombocytopenia suggests a generalized disorder of hematopoiesis caused by toxins (eg, alcohol), nutritional deficit (vitamin $B_{12}$ or folate deficiency), or myelodysplasia. When these findings are present, further diagnostic evaluation may be indicated. Hypochromia (low MCH) likely reflects longstanding iron-deficiency erythropoiesis.

In general, the anemia of CKD is normochromic and normocytic; that is, morphologically indistinguishable from the anemia of chronic disease. It characteristically is hypoproliferative: erythropoietic activity is low, consistent with insufficient erythropoietin stimulation. Proliferative activity is assessed by determination of the absolute reticulocyte count, the reticulocyte index, and the reticulocyte production index. The normal *absolute reticulocyte count* ranges from 40,000 to 50,000 cells/$\mu$L of whole blood. The *reticulocyte index* is calculated from the ratio of observed to normal reticulocyte count. Thus:

$$\text{Reticulocyte index} = \left[\text{observed absolute reticulocyte count}\right] \div \left[\text{normal absolute reticulocyte count}\right]$$

Conversely, the *reticulocyte production index* corrects for the effects of erythropoietin-stimulated early release of reticulocytes from the bone marrow. Early release shortens the fraction of time reticulocytes mature in marrow and proportionally prolongs their maturation time in circulation. The result of early release is an increase in total reticulocyte count. However, that increase reflects the premature shift to the circulation, not increased erythroid production.[94] Normal maturation time in circulation is 1 day. The expected maturation time, presuming a sufficient erythropoietin response to anemia, increases to 1.5 days at Hb values between 10 and 13 g/dL, 2 days at values between 7 and 10 g/dL, and 2.5 days at values between 3 and 7 g/dL. The *reticulocyte production index* is calculated by dividing the reticulocyte index by the expected maturation time. Thus:

$$\text{Reticulocyte production index} = \left[\text{reticulocyte index}\right] \div \left[\text{expected maturation time}\right]$$

In an anemic patient, a reticulocyte production index greater than 3 is evidence of a normal proliferative response to anemia, whereas a pro-

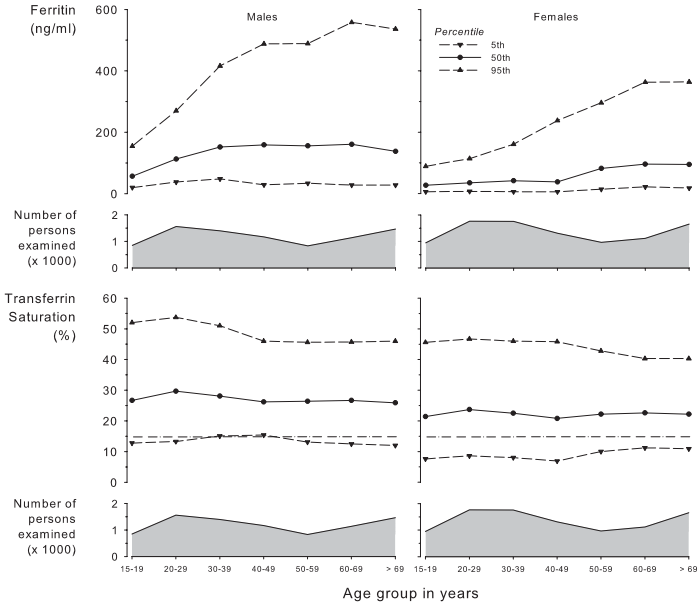


**Fig 12. Distribution of ferritin and TSAT values by age group in males and females. Data are given as 5th, 50th, and 95th percentiles. Centers for Disease Control and Prevention; National Center for Health Statistics, 2005.[40]**

duction index of 2 or less is regarded as hypoproliferative, ie, little or no effective response. Although there is significant between-patient variability in absolute reticulocyte count, the test is sufficiently useful to serve its intended purpose as a semiquantitative marker of erythropoietic activity. The specific utility of the reticulocyte production index for the diagnosis and management of anemia in patients with CKD has not been evaluated.

By contrast, erythropoietin levels are not routinely useful in distinguishing erythropoietin deficiency from other causes of anemia in clinical settings.[18,19,85,95,96]

### *Evaluating Iron Status in Anemic Patients With CKD*

Iron status test results reflect either the level of iron in tissue stores or the adequacy of iron for erythropoiesis. Serum ferritin level is the only available blood marker of storage iron. Tests that reflect adequacy of iron for erythropoiesis include TSAT, MCV, and MCH and the related indices, percentage of hypochromic red blood cells (PHRC) and content of Hb in reticulocytes (CHr). Because long sample transport and storage times spuriously elevate PHRC results, the PHRC test is not suitable for routine use in many patient-care settings. MCV and MCH decrease to less than normal range only after long-standing iron deficiency. Thus, timely and reliable assessment of the adequacy of iron supply for erythropoiesis generally requires results of either TSAT or, when available, CHr. We further recommend testing Hb, ferritin, and TSAT or CHr together because the combination provides important insight into external iron balance and internal iron distribution. The distribution of ferritin and TSAT by age and sex in the general population is shown in Fig 12.

Testing iron status before treating anemia in patients with CKD serves 2 purposes: to assess the potential contribution of iron deficiency to anemia and determine whether further evaluation for sources of gastrointestinal (GI) bleeding is needed. Iron status testing is poorly suited to serve a third purpose, the prediction of responsiveness to iron therapy, because no single iron test or combination of tests discriminates iron-responsive from iron-unresponsive patients and because patients respond to intravenous (IV) iron therapy even when iron status results are substantially greater than the range associated with evidence of iron deficiency (Guideline 3.2).

The potential contribution of iron deficiency to anemia is demonstrated best by examining the relationship between iron status test results and Hb difference from a reference value. Not surprisingly, the nature of the relationship depends on whether the test measures iron stores or iron adequacy for erythropoiesis.

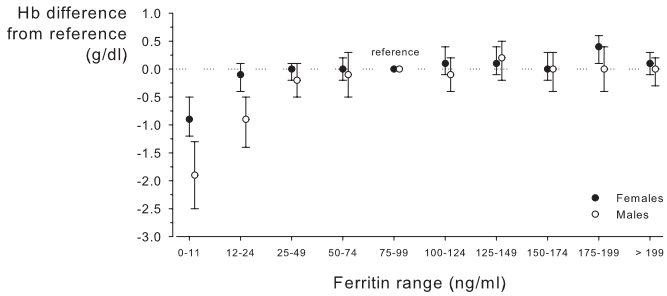


**Fig 13. Distribution of Hb levels by ferritin range in patients with CKD. Results shown as mean 95% ± CI for parameter estimates. Reprinted with permission.[26]**

The relationship between measures of iron stores (serum ferritin) and Hb difference from reference is shown in Fig 13. In patients with ND-CKD, Hb values do not decrease to less than reference level except at the lowest ferritin levels (<25 ng/mL in males and <11 ng/mL in females). These ferritin results closely approximate the fifth percentile of serum ferritin values in a randomly selected population (males ≥ 20 years, 33 ng/mL; females ≥ 60 years, 15 ng/mL; US Renal Data System [USRDS] special data request, NHANES 1999 to 2002 data set) and likely represent sex-specific thresholds at which iron stores are exhausted in patients with ND-CKD.

In patients with HD-CKD, the relationship between serum ferritin and Hb values is less clear, probably because the relationship between ferritin level and iron stores may be disturbed. In relatively healthy patients with HD-CKD before widespread use of IV iron therapy, the finding of a ferritin level less than 50 ng/mL was not uncommon[97] and was associated with absent bone marrow iron in approximately 80% of patients.[98] However, in patients with a greater disease burden, absent iron stores may still be found at ferritin levels approaching or even exceeding 200 ng/mL.[99]

The relationship between adequacy of iron supply for erythropoiesis (from TSAT) and Hb difference from reference in patients with ND-CKD is shown in Fig 14. The relationship between TSAT and Hb values is continuous and relatively linear throughout the encountered range of TSAT values (Fig 14). There is no obvious threshold or cutoff value of TSAT below which the prevalence of anemia is sharply higher or the level of Hb is sharply lower. Hb values are significantly lower than reference (ie, Hb results seen in patients with a TSAT of 20% to 29%) among both males and females only when TSAT is less than 16%. By comparison, analysis of TSAT values in a randomly selected survey population showed that the fifth percentile of TSAT results in males 20 years and older is 12.5%, and that in females 60 years and older is 10.3% (USRDS special data request, NHANES 1999 to 2002 data set).

In short, in patients with ND-CKD undergoing evaluation for anemia, ferritin levels less than 25 ng/mL in males and less than 12 ng/mL in females suggest that storage-iron depletion is contributing to anemia. Serum ferritin level is less reliable in the evaluation of iron stores in patients with HD-CKD than in those with ND-CKD. Iron-deficiency erythropoiesis is most likely to contribute to anemia when TSAT results are less than 16%. However, the clinical utility of TSAT is impaired by the absence of a diagnostic threshold.

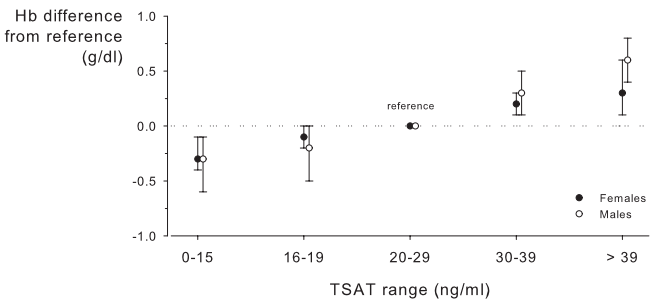


**Fig 14. Distribution of Hb levels by TSAT range in patients with CKD. Results shown as mean ± 95% CI for parameter estimates. Reprinted with permission.[26]**

Although iron status tests provide reasonable markers to detect iron deficits, there is little information to guide what action should be taken in response, particularly in regard to further diagnostic GI workup. In the absence of menstrual bleeding, iron depletion and iron deficiency result from blood loss from the GI tract. GI pathological states—including ulcer disease, colonic polyps, colorectal carcinoma, *Helicobacter pylori* positivity, and sprue—are common among iron-deficient patients referred for esophagogastroduodenoscopy and colonoscopy.[100-103]

Testing for occult blood in stool is not recommended as part of the evaluation of iron-deficient patients.[104,105] As a screening test for colorectal carcinoma or precancerous colonic polyps, stool occult blood testing commonly is performed, but a high false-negative result rate renders it relatively unreliable.[106] However, in a patient with iron deficiency, the test provides no useful information because a positive stool test result only confirms a diagnosis that the blood test results signifying iron deficiency have already established (GI blood loss), while a negative stool test result can only be falsely reassuring.

In patients with CKD, occult blood in stool was found in 6% to 7% of patients with HD-CKD and PD-CKD and nearly 20% of patients with ND-CKD.[107] Among patients with heme-positive stools, follow-up endoscopy identifies GI pathological states (predominantly gastric and duodenal) in approximately 60% of patients. However, because the likelihood of finding GI lesions in patients with CKD with and without heme-negative stools has not been examined, critical information to establish the sensitivity and specificity of occult blood testing in the target population is lacking. Moreover, there is no information comparing the clinical utility of occult blood testing with that of endoscopy in the relevant patient population with iron deficiency, anemia, and CKD or in any target population with iron deficiency. Finally, there is no evidence that either endoscopy or other additional GI imaging improves patient outcomes when routinely conducted for the evaluation of iron deficiency. Thus, although colonoscopy can be part of an age-appropriate cancer screening and esophagogastroduodenoscopy should be strongly considered if iron deficiency is confirmed in an anemic patient with CKD, there is insufficient evidence to recommend their routine use for anemia evaluation.

In conclusion, although epidemiological evidence yields a consistent definition of iron depletion (ferritin $<$ 25 ng/dL) and iron deficiency erythropoiesis (TSAT $<$ 16%), in the absence of sufficient evidence that demonstrates therapeutic consequences based in these threshold values and in the presence of information that therapeutic intervention should be guided by other factors (see Guideline 3.2), these definitions lack specific recommendations for action and thereby fall short of constituting a guideline statement or CPR.

### *Further Evaluation*

These tests are recommended only for the the initial evaluation of anemia. Should initial evaluation yield evidence for disorders other than erythropoietin deficiency or iron deficiency, further evaluation is warranted.

# CPG AND CPR 2.1. HB RANGE

Treatment thresholds in anemia management describe the intended goal of current treatment for the individual patient. The Hb treatment range represents the intended goal of ESA and iron therapy.

**2.1.1 Lower limit of Hb:**
**In patients with CKD, Hb should be 11.0 g/dL or greater. (*MODERATELY STRONG RECOMMENDATION*)**

**2.1.2 Upper limit of Hb:**
**In the opinion of the Work Group, there is insufficient evidence to recommend routinely maintaining Hb levels at 13.0 g/dL or greater in ESA-treated patients.**

## BACKGROUND

Previous (2001) KDOQI Guidelines for the Treatment of the Anemia of CKD[2] incorporated the following lines of evidence to support a recommended Hb target level of 11.0 to 12.0 g/dL in patients with CKD:

- Observational evidence showed that mortality rates were lower in HD patients with Hb values close to this range in comparison to HD patients with lower Hb levels.
- Observational evidence in patients with HD-CKD and those with ND-CKD showed an association between anemia and left ventricular hypertrophy (LVH).
- A reasonable body of evidence from randomized controlled trials (RCTs) comparing distinct Hb level targets suggested that partial correction of anemia, to levels of approximately 11 to 12 g/dL, led to improved QOL.
- A limited body of evidence from distinct-target RCTs suggested that partial correction of anemia, to levels of approximately 11 to 12 g/dL, led to partial regression of LVH.
- A single large RCT examining patients with HD-CKD with patients with overt CVD suggested that Hb level targets of 14 g/dL do not improve the primary study outcome of death or myocardial infarction (MI) and appear to jeopardize dialysis vascular access compared with Hb levels of 10 g/dL.

To develop the current guideline, we undertook a comprehensive reexamination of the available evidence that encompassed both the RCTs previously cited and RCTs published since the previous analysis. Because each RCT included iron agents as an adjunct to ESA, the guideline includes references to both.

## RATIONALE

### *Hb Level Should Be 11.0 g/dL or Greater*

Evidence to support a recommended target Hb level demands the highest order of methodologic rigor. To determine the recommended target Hb level, we confined consideration to results gained from RCTs that enrolled patients who are representative of the key CKD populations (anemia in patients with ND-CKD, PD-CKD, and HD-CD), assigned patients to at least 2 distinct target Hb level groups (treatment versus placebo/control or higher versus lower Hb level), assessed outcomes that are important to patients, and reported results of between-group comparisons. We based our conclusions on evidence that, when taken together, reflected high or at least moderate overall quality. Such evidence has few limitations, shows consistency among trials, bears direct relevance to the anemic CKD population, and lacks sparseness or substantial bias. We gave weight to between-group differences (effect sizes) that are not only statistically significant, but also clinically meaningful, particularly when considering QOL. When weighing evidence of improved outcomes against the potential for increased risk, we sought to determine the Hb level(s) at which a patient can expect an overall net benefit. Finally, we required that the recommended target Hb statement be clear and unambiguous and the target Hb level be achievable in practice.

Evidence supporting the statement that *Hb level should be 11.0 g/dL or greater* includes results from 22 RCTs and is presented both in detail for each trial Table 12 through 19) and in summary for each outcome ( Table 20 and Table 21). The evidence is confined to results of between-group comparisons generated by trials randomizing patients to distinct intent-to-treat Hb targets, using “ESA versus placebo” or “ESA lower Hb target versus ESA higher Hb target” designs (Fig 15). We excluded evidence from observational studies. Cohort-based observa-

## Table 12. RCTs Examining Effects of Distinct Hb Targets/Levels on Key Clinical Outcomes in the HD-CKD and PD-CKD Populations

| Author, Year | N | CKD Stage | Baseline [a] Hb (g/dL) | Follow-up (mo) | Applicability | Arm 1 / Arm 2 / Arm 3 | Mean Hb (g/dL) Target (Achieved) | Clinical Outcomes (Arm 1 vs. Arm 2 vs. Arm 3) | | | | | | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | CVD Events (%) | LVH | Mortality (%) | Hospitalization | Dialysis Adequacy | Transfusion (%) | QOL [b] | |
| *ESA vs. ESA* | | | | | | | | | | | | | | | |
| Besarab, 1998 [108] | 1,233 | HD-CKD | 10.2 | 14 | | ESA High<br>ESA Low | 14.0 (12.7-13.3)<br>10.0 (10.0) | *Nonfatal MI 3.1 vs. 2.3 NS [c] | — | *29.6 vs. 24.4 NS [c] | NS | ΔKt/V: –0.03 vs. +0.06 P <0.001 | 21 vs. 31 P = 0.001 | See QOL Table | ● |
| Parfrey, 2005 [109] | 596 | HD-CKD | 11.0 | 24 | | ESA High<br>ESA Low | 13.5-14.5 (13.3)<br>9.5-11.5 (10.9) | CVA: 4 vs. 1 P = 0.045 Other CVD: NS | *NS | NS | — | ΔURR: 0 vs. +2 % P <0.05 | — | See QOL Table | ● |
| Foley, 2000 [110] | 146 | HD-CKD | 10.4 | 11 | | ESA High<br>ESA Low | 13-14 (13)<br>9.5-10.5 (10.5) | NS | *NS | NS | — | Kt/V: NS[h] | — | See QOL Table | ● |
| CanEPO, 1990-1991 [49, 117] | 118 | HD-CKD | 7.0 | 6 | | ESA High<br>ESA Low<br>Placebo | 11.5-13 (11.7)<br>9.5-11 (10.2)<br>(7.4) | — | — | NS | — | — | 3 vs. 3 vs. 72 ESA vs. Placebo: P <0.05 [f] | *High vs. Low: NS<br>ESA vs. Placebo: P = 0.024 | ● |
| Furuland, 2003 [118] | 416 | 4-5 PD-CKD HD-CKD [d] | 10.9 | 12 | | ESA High<br>ESA Low | 13.5-16.0 (3.6)<br>9-12 (11.3-11.7) | — | — | NS | NS | — | — | *See QOL Table | ○ |
| Suzuki, 1989 [119] | 179 | HD-CKD | 6.3 | 2 | | ESA High [e]<br>ESA Low<br>Placebo | <11 (8.7)<br>(8.2)<br>(6.1) | — | — | — | — | — | 8 vs. 5 vs. 23 ESA vs. Placebo: P <0.05 | See QOL Table | ○ |
| Furuland, 2005 [120] Substudy of Furuland, 2003 | 24 | HD-CKD | 11.1 | 5.5 | | ESA High<br>ESA Low | 13.5-16.0 (14.3)<br>9-12 (10.9) | — | — | — | — | ΔKt/V: –0.1 vs. 0 nd | — | — | ○ |
| McMahon, 1999,2000 [121, 122] | 14 | HD-CKD | 8.5 | 1.5 | | ESA High [e]<br>ESA Low | 14 (14)<br>10 (10) | --- | — | — | — | — | — | P <0.02 | ○ |

| Author, Year | N | CKD Stage | Baseline [a] Hb (g/dL) | Follow-up (mo) | Applicability | Arm 1 / Arm 2 / Arm 3 | Mean Hb (g/dL) Target (Achieved) | Clinical Outcomes (Arm 1 vs. Arm 2 vs. Arm 3) | | | | | | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | CVD Events (%) | LVH | Mortality (%) | Hospitali-zation | Dialysis Adequacy | Transfusion (%) | QOL [b] | |
| *ESA vs. Placebo* | | | | | | | | | | | | | | | |
| Nissenson, 1995 [123] | 152 | PD-CKD | 8 | 6-9 | | ESA | 10.7-12.7 (11.2) | — | — | NS | — | — | ΔU/pt/4 wk –0.21 vs. +0.42 P <0.05 | — | ⊙ |
| | | | | | | Placebo | (8.0) | | | | | | | | |
| Bahlmann, 1991 [124] | 129 | HD-CKD | 7.7 | 6 | | ESA | 10-11.7 (10.6-10.9) | NS | — | NS | — | — | 9 vs. 60 P <0.05 | — | ⊙ |
| | | | | | | Placebo | (7.8) | | | | | | | | |
| Sikole, 1993 [125] | 38 | HD-CKD | 6.7 | 12 | | ESA [e] | 10-11.7 (11.3) | — | *LVEDd (mm) 48 vs. ↑ 53 P = 0.002 | — | — | — | — | — | ⊙ |
| | | | | | | Control | (8.3) [g] | | | | | | | | |
| *ESA vs. Placebo in Pediatric Patients* | | | | | | | | | | | | | | | |
| Morris, 1993 [126] | 11 | PD-CKD HD-CKD | 7.3 | 6 | | ESA | 10.5-12 (11.2) | — | — | — | — | — | — | *See QOL Table | ○ |
| | | | | | | Placebo | (7) | | | | | | | | |

**Footnotes:**

* Primary Outcome, if clearly indicated.

a. All baseline data given for arm 1, unless otherwise specified.

b. Global Scores, if documented, are provided here. Refer to Tables 13 and 19 for details of QOL measurements.

c. The primary outcome was a composite of nonfatal MI or death. RR 1.3, 95% CI 0.9-1.8, P>0.05.

d 294 HD-CKD, 51 PD-CKD, 72 ND-CKD patients.

e. Iron cointervention not documented.

f. Data at 8 weeks.

g. Median.

h. LVD subgroup: Kt/V 1.41 vs.1.50, P=0.025

**Coding of Outcomes:**

Mortality: All-cause mortality.

CVD Event: Includes CHF exacerbation, MI, arrhythmias, angina, interventional procedure such as CABG or angioplasty, sudden death, CVA.

LVH: As identified by echocardiography with minimum of 6 month follow-up.

**Table 13. RCTs Examining Effects of Distinct Hb Targets/Levels on QOL in the HD-CKD and PD-CKD Populations**

| Author, Year | N | CKD Stage / Baseline Hb (g/dL) | Follow-up (mo) | Applicability | Arm 1 / Arm 2 / Arm 3 | Mean Hb (g/dL) Target (achieved) | Primary Outcome of Study | QOL (Arm 1 vs. Arm 2 vs. Arm 3 ) | | | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Scale/Test | Global QOL | Vitality and Fatigue | Other Measures of QOL | |
| Parfrey, 2005 [109] | 324 | 5 (HD)<br>11.0 | 24 | ⚥ a | ESA High<br>ESA Low | 13.5-14.5 (13.1)<br>9.5-11.5 (10.8) | LV volume index | KDQOL subscales: SF-36 Vitality and Quality of Social Interaction | | SF-36 Vitality: + | Social Interaction: NS | ● |
| | | | | | | | | FACIT Fatigue Scale | NS | | | |
| CanEPO, 1990-1991 [49, 117] | 118 | 5 (HD)<br>7.0 | 6 | ⚥ b | ESA High<br>ESA Low<br>Placebo | 11.5-13 (11.7)<br>9.5-11 (10.2)<br>(7.4) | QOL and functional capacity [c] | KDQ | | Fatigue: + | Physical: +<br>Relationships: +<br>Depression: +<br>Frustration: NS | ● |
| | | | | | | | | SIP | + | | Physical: +<br>Psychosocial: NS | |
| | | | | | | | | TTO | | | NS | |
| Besarab, 1998 [108] | 1,233 | 5 (HD)<br>10.2 | 14 | ⚥ | ESA High<br>ESA Low | 14.0 (12.7-13.3)<br>10.0 (10.0) | Mortality and nonfatal MI | SF-36 | | | Physical: + [d] | ● |
| Foley, 2000 [110] | 94 | 5 (HD)<br>10.1 | 12 | ⚥ e | ESA High<br>ESA Low | 13-14 (13)<br>9.5-10.5 (10.5) | ΔLV mass index in individuals with concentric LVH; Δ cavity volume index in individuals with LVD | KDQ [f] | | Fatigue: + | Physical Symptoms: NS<br>Depression: +<br>Relationships: +<br>Frustration: NS | ● |
| | | | | | | | | SF-36 | | Vitality: NS | Physical Function: NS<br>General Health: NS<br>Bodily Pain: NS<br>Social Functioning: nd<br>Emotional Role: nd<br>Mental Health: nd | |
| | | | | | | | | HUI | | | Mean HUI = 0.81 (CI: 0.78, 0.85) | |
| Furuland, 2003 [118] | 253 | 4-5 (PD,HD)<br>10.9 | 12 | ⚥ | ESA High<br>ESA Low | 13.5-16.0 (13.6)<br>9-12 (11.4) | QOL and safety | KDQ | | Fatigue: NS [g] | Physical: +<br>Relationship: NS<br>Depression: +<br>Frustration: NS [g] | ○ |
| McMahon, 1999, 2000 [121, 122] | 14 | 5 (HD)<br>8.3 | 1.5 | ⚥ | ESA High<br>ESA Low | 14 (14)<br>10 (10) | Several primary outcomes, including QOL and exercise performance | SIP | + | | Physical: NS<br>Psychosocial: + | ○ |

| Author, Year | N | CKD Stage / Baseline Hb (g/dL) | Follow-up (mo) | Applic-ability | Arm 1 / Arm 2 / Arm 3 | Mean Hb (g/dL) Target (achieved) | Primary Outcome of Study | QOL (Arm 1 vs. Arm 2 vs. Arm 3 ) | | | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Scale/Test | Global QOL | Vitality and Fatigue | Other Measures of QOL | |
| *Pediatric Patients* | | | | | | | | | | | | |
| Morris, 1993 [126] | 10 | 5 (PD,HD) / 7.0 | 8 | | ESA / Placebo | 10.5-12 (11.2) / (6.5) | QOL, diet, exercise tolerance, and PD efficiency | 25-part Parental Questionnaire [h] | NS | Physical Performance/ General Health (includes school attendance): + | Sleep: NS / Diet: NS / School Performance: NS / Psychosocial: NS | ○ |

**Footnotes:**

a. No CVD or LVD.
b. All individuals had LVD or LVH at baseline, no CVD.
c. Data shown for ESA arms vs. Placebo. All statistical comparisons for ESA High vs. ESA Low were not significant.
d. Increased by 0.6 point for each percentage point increase in Hct.
e. Free of marked comorbidity.
f. Results given are from repeated measures analysis of variance.
g. P = 0.05
h. 25-Part Parental Questionnaire, modified from a previously used questionnaire[126]. Questions covered various aspects of the child's well-being and behavior, including mood and psychological behavior, social interaction, somatic complaints and general health, sleep, diet, school functioning, and physical performance.

**Coding of Outcomes**:

Coding of comparison of study arm 1 versus study arm 2: (+) better, (–) worse with reference to benefit for patient.

**Key to QOL Measurement Scales/Tests:**

*36-item Medical Outcomes Study Short-Form Health Survey (SF-36)*: Evaluates eight health-related aspects: physical function, social function, physical role, emotional role, mental health, energy, pain, and general health perceptions. Each portion of the test is scored on a scale that ranges from 0 (severe limitation) to 100 (no limitation).

*Center for Epidemiologic Studies Depression Scale (CESDS):* Has been used extensively in epidemiological studies of the general community and chronic disease populations. It is scored from 0 to 60, with higher scores indicating a greater number of depression symptoms.

*Functional Assessment of Chronic Illness Therapy (FACIT)*: Collection of QOL questionnaires targeted to the management of chronic illness

*Health Utilities Index (HUI)*: Provides an overall index of health, derived from scores in 7 aspects: sensation, mobility, emotion, cognition, self-care, pain, and fertility. This is an interval scale that can vary in theory between 0 (death) and 1 (perfect health).

*Karnofsky Performance Scale (KPS)*: Uses 10 steps with scores ranging from 100 (normal, without any limitation) to 10 (moribund) as an overall indicator of functional ability and self-sufficiency. It is considered an objective quality-of-life indicator.

*Kidney Disease Quality of Life (KDQOL)*: Validated in dialysis patients. The Short Form (SF) version used for assessment of vitality.

*Kidney Diseases Questionnaire (KDQ)*: Is validated in dialysis patients. Contains 26 questions divided into 5 sections: patient-specific physical symptoms, fatigue, depression, relationships, and frustration. All questions are scored on a 7-point Likert scale (7 = no problem, 1 = severe problem).

*Quality of American Life (QoAL)*: Asks the patient to rate his or her satisfaction with life on a scale from 1 to 7, with higher scores indicating greater satisfaction.

*Renal Quality of Life Profile (RQoLP):* Instrument based on constructs representing renal patient's own QOL determinants.

*Sickness Impact Profile (SIP):* Is a behavior-related questionnaire that evaluates non–disease-specific, sickness-related behavioral dysfunction. It is widely used for end-stage renal disease patients and in studies evaluating quality-of-life improvement with ESA treatment for end-stage renal disease-related anemia. The SIP includes 136 items grouped into 12 categories of activity in physical and psychological dimensions. Scores range from 0 (no behavioral dysfunction) to 100 (100% dysfunction in a category or group). Unlike the KPS and the KDQ, lower scores for the SIP indicate better QOL.

*Time Trade-off (TTO)*: Is a unidimensional measure of QOL that gives a value to a patient's QOL ranging from 1.0 (full health) to 0 (patient is indifferent between life and death). This is a utility measure using the time trade-off hypothesis.

**Table 14. Non-CVD/Mortality AE Rates in RCTs Examining Distinct Hb Targets/Levels in HD-CKD and PD-CKD Populations: ESA versus ESA**

| Author, Year | N | Dialysis Modality | Description of Intervention | Follow-up (mo) | Arm 1 / Arm 2 / Arm 3 | Mean Hb (g/dL) Target (achieved) | AEs (Arm 1 vs. Arm 2 vs. Arm 3) | | | | | | Total D/C of Drug |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | BP Change or Hypertension | | Access Thrombosis (%) | | Seizures | Other Reported AE [a] | |
| | | | | | | | Definition | Outcome | Definition | Outcome | | Description and Results | |
| Besarab, 1998 [108] | 618 | HD [b] | IV or SC ESA 1.5X pretrial dose; adjusted after 2 wk | 14 | ESA High | 14.0 (12.7-13.3) | Mean SBP and DBP during the study [c] | NS | Both AV graft and AV fistulae | 39% vs. 29% (P = 0.001) | NS | — | 0 |
| | 615 | | IV or SC ESA adjusted | | ESA Low | 10.0 (10.0) | | | | | | | 0 |
| Parfrey, 2005 [109] | 284 | HD | IV or SC ESA for 24 wk to reach target then maintained for 72 wk | 24 | ESA High | 13.5-14.5 (13.3) | Hypertension not specified | NS | AV fistulae, permanent catheter, non-site specific embolism | 23% vs. 19% (NS) | — | Overall treatment emergent AE in ≥10% of patients: 96% vs. 94% [d] | nd |
| | 281 | | | | ESA Low | 9.5-11.5 (10.9) | | | | | | | |
| Furuland, 2003 [118] | 216 | HD PD [e] | SC ESA TIW | 12 | ESA High | 13.5-16.0 (13.4-14.3) | Δ mean DBP from baseline | 90 vs. 83 mm Hg (P = 0.02) | Complication in AV graft, AV fistulae or catheter during study | 5% vs. 2% in HD patients only (NS) | — | Individuals with at least 1 SAE NOS: 51% vs. 38.5% (NS) Thromboembolic: Event: 56 vs. 47 per arm (NS) [f] | 34 |
| | 200 | | SC ESA TIW or no treatment | | ESA Low | 9-12 (11.3-11.7) | | | | | | | 15 |
| Suzuki, 1989 [119] | 59 | HD | IV ESA 3,000 IU TIW | 2 | ESA High | <11 (8.7) | Increased dose of anti-HTN meds | 5 vs. 4 vs. 1 individuals | — | — | — | No. of AE NOS 6.7% vs. 8.3% vs. 1.7% per arm [g] | nd [h] |
| | 58 | | | | ESA Low | (8.2) | | | | | | | |
| | 57 | | | | Placebo | (6.1) | | | | | | | |
| Foley, 2000 [110] | 73 | HD | SC ESA ESA high arm had a 24 wk "ramping" phase. 24 wk maintenance was similar in both arms | 11 | ESA High | 13-14 (13) | Mean SBP, DBP, during between groups, and use of anti-HTN meds | For LVH: significant SBP and ↑ anti-HTN For LVD: NS | AV access | 8% vs. 14% (NS) [i] | — | — | nd |
| | 73 | | | | ESA Low | 9.5-10.5 (10.5) | | | | | | | |
| Abraham, 1991 [127] | 39 | HD | IV ESA TIW after HD session 25, 100 or 200 IU/kg | 2.5-4.5 | ESA 200 U/kg | (11.6) | % of individuals with increases in DBP ≥10 mm Hg and/or anti-HTN meds | 56% vs. 52% vs. 45% (NS) | — | — | — | — | nd |
| | 40 | | | | ESA 100 U/kg | (11.0) | | | | | | | |
| | 42 | | | | ESA 25 U/kg | (8.8) | | | | | | | |

| Author, Year | N | Dialysis Modality | Description of Intervention | Follow-up (mo) | Arm 1 / Arm 2 / Arm 3 | Mean Hb (g/dL) Target (achieved) | AEs (Arm 1 vs. Arm 2 vs. Arm 3) | | | | | | Total D/C of Drug |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | BP Change or Hypertension | | Access Thrombosis (%) | | Seizures | Other Reported AE [a] | |
| | | | | | | | Definition | Outcome | Definition | Outcome | | Description and Results | |
| CanEPO 1990 [49] | 38 | HD | IV ESA 100 IU/kg initial dose; titrated to achieve targets | 6 | ESA High | 11.5-13 (11.7) | Severe HTN required withdrawal [j] | 5% vs. 5% vs. 0% (P = 0.01) | AV graft or AV fistulae clotting | # of Events: 7 vs. 4 vs. 1 (P = 0.01) | 0% vs. 5% vs. 2.5% (NS) | Nonspecific AEs: 63 vs. 61 vs. 65 per arm [k] | 2 |
| | 40 | | | | ESA Low | 9.5-11 (10.2) | | | | | | | 2 |
| | 40 | | | | Placebo | (7.4) | | | | | | | 0 |
| Berns, 1999 [128] | 14 | HD | ESA to maintain target | 12 | ESA High | 14 (14.0) | HTN: SBP >140 mm Hg, DBP >90 mm Hg; or Δ anti-HTN meds. | Slightly more prevalent in Low vs. High (NS) | — | — | — | — | nd |
| | 14 | | | | ESA Low | 10 (10.1) | | | | | | | |
| McMahon, 1999, 2000 (Crossover) [121, 122] | 8 | HD | SC ESA 2x/wk if total dose <20,000 IU/wk; IV ESA TIW if total dose >20,000 IU/wk | 1.5 | ESA High | 14 (14.0) | Mean ABP for peak day and nocturnal readings taken before and after HD | NS | — | — | — | — | 0 |
| | 6 | | | | ESA Low | 10 (10) | | | | | | | 0 |

**Footnotes:**

a. For "Other Reported AE" column, outcomes may be recorded in no. of events per arm, no. of events per patient, or % given heterogeneity in reporting.
b. All individuals had evidence of CHF and IHD.
c. Prestudy ABP had to be below 160/100 for 4 weeks prior to study. Subgroup analysis[129]: 31 patients; mean day & nocturnal BP readings for 24 hr were NS at baseline or at follow-up.
d. Of these P >0.05 for all comparisons except headache was greater in the ESA High arm and skeletal pain and surgery were greater in ESA Low arm.
e. Includes some predialysis patients, Stages 4-5 CKD.
f. Thromboembolic events were defined by WHO classification.
g. 7 of 10 continued treatment.
h. Not documented per arm. 3 individuals receiving ESA discontinued treatment.
i. Patients with ongoing access problems were specifically excluded. The event rates were small and study did not have enough statistical power to detect a moderate impact on access thrombosis; the proportion using natural fistulae in the Besarab study was 23% compared to 76% in this study.
j. DBP was increased in patients on ESA compared to placebo. P = 0.001; no statistical difference between High ESA and Low ESA.
k. Nonspecific events include: clotting of tubing in dialysis machine, flu-like symptoms, headache, red eye, epistaxis or hemorrhage, pain in chest, abnormal sense of taste, aches in bone and muscle.

**Coding of Outcomes:** (Variable per Column Description)
Hypertension: Includes mean changes in SBP, DBP, MAP, increase in use of anti-HTN medications, difficult to control hypertension.
Access Thrombosis: Synthetic grafts and fistulae.

## Table 15. Non-CVD/Mortality AE Rates in RCTs Examining Distinct Hb Targets/Levels in the HD-CKD and PD-CKD Populations: ESA vs. Placebo

| Author, Year | N | Dialysis Modality | Description of Intervention | Follow-up (mo) | Arm 1 / Arm 2 | Mean Hgb (g/dL) Target (achieved) | AEs (Arm 1 vs. Arm 2) | | | | | | Total D/C of Drug |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | BP Change or HTN | | Access Thrombosis (%) | | Seizures | Other AE[a] | |
| | | | | | | | Definition | Outcome | Definition | Outcome | | Description and Results | |
| Abraham, 1991 [127] | 151 / 78 | HD | IV ESA TIW after HD session 100 IU/kg | 2-3 | ESA / Placebo | 12.5-13.5 (10.8) / (7.5) | Correlation between BP and change in Hb or rate of Hb rise | No correlation[b] ESA arm: 1 individual withdrawn for severe high BP | — | — | 3 vs. 0 individuals | — | nd |
| Nissenson, 1995 [123] (Crossover) | 78 / 74 | PD | Self-admin. SC ESA TIW Blinded phase: 4,000 IU/mL; Maintenance phase: 2,000, 4,000, or 10,000 IU/mL | 6-9 | ESA / Placebo | 10.6-12.6 (11.2) / (8.0) | Increased DBP and anti-HTN Regimen | 55% vs. 20% | — | — | — | Mild and serious AEs: 407 AE in 74 patients vs. 325 AE in 63 patients[c] | nd |
| Bahlmann 1991 [124] | 53 / 46 | HD | IV ESA each HD session Blinded Phase (4 wk): 80 IU/kg/wk to target; Maintenance phase: 40 IU/kg/wk | 6 | ESA / Placebo | 10-11.7 (10.6) / (7.8) | HTN: SBP ≥160 mm Hg or DBP ≥95 mm Hg or anti-HTN therapy initiated or intensified | 28% vs. 11% | Clot of AV fistula | 9% vs. 9% | 0 vs. 0 | Infection events: 20 vs. 10[d] | 0 / 0 |

**Footnotes:**

a. For "Other AEs" column, outcomes may be recorded in no. or % of events per arm, no. or % of events per patient, or % given heterogeneity in reporting.

b. No significant correlation but clinically important increases in BP appeared dose-related with earlier time to peak and peak BP achieved.

c. Mild and severe reactions if not otherwise specified. Of 408 such events in ESA group, 37% (N = 149) were considered mild but possibly related to study medication, 1% (N = 5) were considered severe or life-threatening, possibly or definitely related to study medication. In the placebo group 26% (N = 85) were considered mild but possibly related to study medication, <1% (N = 2) were considered severe or life-threatening, possibly or definitely related to study medication.

d. More infections in ESA group, but only with URTI/viral; only pneumonias seen in Control.

**Coding of Outcomes:** Variable per Column Description

Hypertension: Includes mean changes in SBP, DBP, MAP, increase in use of anti-HTN medications, difficult to control HTN.

Access Thrombosis: Synthetic grafts and fistulae.

## Table 16. Effects of Distinct Hb Targets/Levels on Key Clinical Outcomes in the ND-CKD Population

| Author, Year | N | CKD Stage | Baseline[a] Hb (g/dL) | Follow-up (mo) | Applicability | Arm 1 / Arm 2 / Arm 3 | Mean Hb (g/dL) Target (Achieved) | Clinical Outcomes (Arm 1 vs. Arm 2 vs. Arm 3) | | | | | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | CVD Events | LVH | Mortality | Kidney Disease Progression | Trans-fusions | QOL[b] | |
| *ESA vs. ESA* | | | | | | | | | | | | | | |
| Levin, 2005 [130A] | 152 | 3-4 | 11.8 | 24 | 🧍🧍🧍 | Early ESA | 12-14 (12.8) | NS | *Δ LVMI: NS | NS[c] | Δ eGFR: NS<br>Incident dialysis: NS | — | — | ● |
| | | | | | | Late ESA | 9-10.5 (11.5) | | | | | | | |
| Roger, 2004 [38] | 127 | 3-4 | 11.2 | 24 | 🧍🧍 | ESA High | 12-13 (12.1) | — | NS*[d] | — | NS | — | NS | ● |
| | | | | | | ESA Low | 9-10 (10.8) | | | | | | | |
| Lim,1989 [131] | 14 | 4-5 | 9.1 | 2 | 🧍 | ESA 150 IU/kg TIW | (13.7) | — | — | 0 | NS | — | — | ○ |
| | | | | | | ESA 100 IU/kg TIW | (12.0) | | | | | | | |
| | | | | | | ESA 50 IU/kg TIW | (11.7) | | | | | | | |
| | | | | | | Placebo | (8) | | | | | | | |
| *ESA vs. Placebo/Control* | | | | | | | | | | | | | | |
| Roth, 1994 [81]<br>Revicki, 1995 [132] | 83 | 4-5 | 8.9 | 11 | 🧍🧍 | ESA | 11.7 (11.2) | NS | — | NS | Δ eGFR*: NS<br>Incident dialysis: NS | NS | See QOL Table* | ● |
| | | | | | | Control | (8.7) | | | | | | | |
| Kuriyama, 1997 [82] | 73 | 3-5 | 9 | 14-36 | 🧍🧍 | ESA | 11.0-11.7 (11.8) | — | — | NS | Doubling $S_{Cr}$*:<br>52% vs. 84%<br>P < 0.05<br>Incident dialysis:<br>33% vs. 65%<br>P = 0.008 | — | — | ◐ |
| | | | | | | Control | (8.4) | | | | | | | |
| Kleinman, 1989 [133] | 14 | 1-3 | 9.4 | 3 | 🧍 | ESA | 12.7-13.3 (11.9) | NS | — | NS | $1/S_{Cr}$: NS | — | — | ◐ |
| | | | | | | Placebo | (9.4) | | | | | | | |
| Clyne, 1992 [73] | 20 | 4-5 | 8.6 | 3 | 🧍 | ESA | 10.0 (11.7) | — | — | — | NS*[e] | — | — | ○ |
| | | | | | | Control | (9.4) | | | | | | | |
| Watson, 1990 [134] | 11 | 5 | 9.7 | 3 | 🧍 | ESA | 12.6 (11.7) | — | — | — | Accelerated renal failure: 2 vs. 0 Nd | — | — | ○ |
| | | | | | | Placebo | (8.7) | | | | | | | |
| Abraham, 1990 [135] | 8 | 3-5 | 10.0 | 2-3 | 🧍 | ESA | 12.3-13.3 (12.3) | — | — | — | $\Delta S_{Cr}$*: NS | — | — | ○ |
| | | | | | | Placebo | (9.6) | | | | | | | |

**Footnotes:**

* Primary outcome, if clearly indicated.

a. All baseline data given for arm 1, unless otherwise specified.

b. Global Scores, if documented, are provided here. Refer to Hb Targets QOL Table for details of QOL measurements.

c. All AEs leading to death were determined to be unrelated to the study drug.

d. Prepower calculation: sample size of 75 patients/treatment arm needed to detect difference in LVMI of 15 g/m² at P = 0.05 (2-sided CI) with 80% power. Number actually analyzed at 2-year follow-up was less in each arm

e. Within arm.

**Coding of Outcomes:**

Mortality: All-cause mortality.

CVD Event: Includes CHF exacerbation, MI, arrhythmias, angina, interventional procedure such as CABG or angioplasty, sudden death.

LVH: As identified by ECHO with minimum of 6 month follow-up.

## Table 17. RCTs Examining Effects of Distinct Hb Targets/Levels on QOL in the ND-CKD Population

| Author, Year | N | CKD Stage / Baseline Hb (g/dL) | Follow-up (mo) | Applic-ability | Arm 1 / Arm 2 | Mean Hb (g/dL) Target (achieved) | Primary Outcome of Study | QOL (Arm 1 vs. Arm 2) | | | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Scale/Test | Global QOL | Vitality and Fatigue | Other Measures of QOL | |
| Roger, 2004 [38] | 155 | 3-4 / 11.2 | 24 | ♀♀[a] | ESA High / ESA Low | 12-13 (12.1) / 9-10 (10.8) | Change in LV mass | SF-36 | NS | | Physical Health: NS<br>Mental Health: NS | ● |
| | | | | | | | | RQOLP | NS | | | |
| Revicki, 1995 [132]<br>Roth, 1994 [81] | 35 | 4-5 / 8.9 | 12 | ♀♀ | ESA / Control | 11.7 (11.2) / (9.0) | Health-related QOL[b] | Selected SIP Scales | | | Home Management: NS<br>Alertness Behavior: NS<br>Social Interaction: NS | ○ |
| | | | | | | | | Selected SF-36 Scales | | Energy: + | Physical Function: +<br>Role Function: NS<br>Health Distress: NS | |
| | | | | | | | | QoAL | | | NS | |
| | | | | | | | | CESDS | | | NS | |
| | | | | | | | | Sexual Dysfunction Interview | | | NS | |

**Footnotes**:

a. Excluded patients with unstable or poorly controlled angina, severe CHF (grade III-IV), severe chronic respiratory disease, symptomatic peripheral vascular disease, or a created arteriovenous fistula.

b. The interview incorporated dimensions of HRQL identified to cover the expected effects of ESA therapy and anemia in predialysis CKD patients based on review of medical literature and discussions with nephrologists and nurses. The intent was to comprehensively measure broad areas of functioning and well-being.

**Key for QOL Scales:**

*36-item Medical Outcomes Study Short-Form Health Survey (SF-36)*: Evaluates 8 health-related aspects: physical function, social function, physical role, emotional role, mental health, energy, pain, and general health perceptions. Each portion of the test is scored on a scale that ranges from 0 (severe limitation) to 100 (no limitation).

*Renal Quality of Life Profile (RQOLP)*: Instrument based on constructs representing renal patient's own QOL determinants.

*Sickness Impact Profile (SIP)*: Established generic health status measure of disability associated with chronic illness.

*Quality of American Life Survey (QoAL)*: Is a life satisfaction scale from Campbell et al. The Quality of American Life. New York, NY, Russell Sage Foundation, 1976.

*Center for Epidemiologic Studies Depression Scale (CESDS)*: Has been used extensively in epidemiological studies of the general community and chronic disease populations. It is scored from 0 to 60, with higher scores indicating a greater number of depression symptoms.

## Table 18. Non-CVD/Mortality AE Rates in RCTs Examining Distinct Hb Targets/Levels in the CKD Population

| Author, Year Study Design | N | CKD Stage | Description of Intervention | Follow-up (mo) | Arm 1 / Arm 2 / Arm 3 | Mean Hb (g/dL) Target (achieved) | AEs: BP Change or HTN — Definition | AEs: BP Change or HTN — Outcome | AEs: Any Non-CVD/Mortality AE [a] — D/C of Drug or Withdrawal (N/Arm) | AEs: Any Non-CVD/Mortality AE [a] — Reason for D/C or Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|
| *ESA vs. ESA* | | | | | | | | | | |
| Levin, 2005 [130A] | 85 | 3-4 | SC ESA 2,000 IU once weekly | 24 | Early ESA | 12-14 (12.8) | Individuals with at least 1 recorded BP >140/90 [b] | 51% | nd | — |
| | 87 | | SC ESA 2,000 IU once weekly if Hb <9.0 g/dL | | Late ESA | 9-10.5 (11.5) | | 54% | | |
| Roger, 2004 [38] | 75 | 3-4 | SC ESA | 24[c] | ESA High | 12-13 (12.1) | 2-yr adjusted mean systolic and diastolic BP between high and low ESA arms | Systolic: NS Diastolic: 81 vs. 78 (P = 0.009) | 0 | — |
| | 80 | | SC ESA if Hb <9 g/dL | | ESA Low | 9-10 (10.8) | | | 3 | nd |
| Lim,1989 [131] | 4 | 4-5 | IV ESA 50, 100 or 150 IU/kg TIW | 2 | ESA 150 | (13.7) | — | — | 0 | — |
| | 4 | | | | ESA 100 | (12.0) | | | 0 | — |
| | 3 | | | | ESA 50 | (11.7) | | | 0 | — |
| | 3 | | | | Placebo | (8) | | | 1 | Seizure |
| *ESA vs. Placebo* | | | | | | | | | | |
| Roth, 1994 [81] | 43 | 1-3 | SC ESA 50 IU/kg/wk, which could be increased by 75 IU/kg/wk; adjusted monthly | 12 | ESA | 11.7(11.2) | Reported HTN Not otherwise specified | 26% | 1 | Individual with nausea, vomiting, GI bleeding |
| | 40 | | | | Placebo | (8.7) | | 10% | 0 | |
| Clyne, 1992 [73] RCT | 12 | 4-5 | ESA dose of 300 IU/kg maintained until Hct ↑10% of initial value or stabilized at Hct >30% | 3 | ESA | 10.0 (11.7) | ↑ in SBP by 10 mm Hg or more, or ↑ in DBP by 5 mm Hg, or made adjustments to anti-HTN medications | 67% | 4 | ESA stopped until BP controlled |
| | 8 | | | | Placebo | (9.4) | | 38% | 0 | — |
| Kleinman, 1989 [133] | 7 | 1-3 | SC ESA 100 IU/kg TIW | 3 | ESA | 12.7-13.3 (11.9) | Δ in anti-HTN medication over the 3-month and Δ mean in SBP, DBP during study | NS | 0 | — |
| | 7 | | | | Placebo | (9.4) | | NS | 0 | — |
| Watson, 1990 [134] | 5 | 5 | SC ESA 100 IU/kg TIW | 3 | ESA | 12.6 (11.7) | Mean BP during trial | No increase with ESA treatment | 2 | Patients withdrew because of suspected acceleration of renal failure |
| | 6 | | | | Placebo | (8.7) | | | 0 | — |
| Abraham, 1990 [135] | 4 | 3-5 | IV or SC ESA 50-150 IU/kg TIW | 1.9 | ESA | 12.3-13.3 (12.3) | Increase in anti-HTN medications | 50% | nd | — |
| | 4 | | | | Placebo | (9.6) | | 50% | | |

**Footnotes:**

a. Any non-CVD/mortality-related AE that required discontinuation of drug or resulted in withdrawal from study.

b. Statistically significant difference in Δ DBP between arms (P=0.027). However, baseline DBP was higher in Late ESA group. There were 4 episodes of hypertension as an AE. None were attributed to the study drug and all were resolved

c. Or until RRT.

## Table 19. RCTs Examining Effects of Distinct Hb Targets/Levels on Exercise Capacity in the HD-CKD and PD-CKD Populations

| Author, Year | N | CKD Stage / Baseline Hb (g/dL) | Follow-up (mo) | Applic-ability | Arm1 / Arm 2 / Arm 3 | Mean Hb (g/dL) Target (achieved) | Primary Outcome of Study | QOL (Arm 1 vs. Arm 2 vs. Arm 3) | | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Scale/Test | Description | Results | |
| Parfrey, 2005 [109] | 324 | 5 (HD) / 11.0 | 24 | 👥 [a] | ESA High / ESA Low | 13.5-14.5 (13.1) / 9.5-11.5 (10.8) | LV volume index | 6-min Walk Test | Patients are asked to cover as much distance in an enclosed corridor as they can in 6 minutes | NS | ● |
| CanEPO, 1990-1991 [49, 117] | 118 | 5 (HD) / 7.0 | 6 | 👥 [b] | ESA High / ESA Low / Placebo | 11.5-13 (11.7) / 9.5-11 (10.2) / (7.4) | QOL and functional capacity [c] | Naughton Stress Test | Treadmill | NS | ● |
| | | | | | | | | 6-min Walk Test | Patients are asked to cover as much distance in an enclosed corridor as they can in 6 minutes | NS | |
| McMahon, 1999, 2000 [121, 122] | 14 | 5 (HD) / 8.3 | 1.5 | 🧍 | ESA High / ESA Low | 14 (14) / 10 (10) | Several primary outcomes, including QOL and exercise performance | Exercise Test [d] | Peak heart rate | NS | ○ |
| | | | | | | | | | Peak $O_2$ consumption | + | |
| | | | | | | | | | Work done | + | |
| *Pediatric Patients* | | | | | | | | | | | |
| Morris, 1993 [126] | 10 | 5 (PD,HD) / 7.0 | 8 | 👥 | ESA / Placebo | 10.5-12 (11.2) / (6.5) | QOL, diet, exercise tolerance, and PD efficiency | Exercise Tolerance Test | 2-min walking | NS [e] | ○ |
| | | | | | | | | | Treadmill | NS [f] | |

**Footnotes:**
a. No CVD or LVD.
b. All individuals had LVD or LVH at baseline, no CVD.
c. Data shown for ESA arms vs. Placebo. All statistical comparisons for ESA High vs. ESA Low were not significant.
d. With cycle ergometer.
e. Not a significant improvement but did improve over study time.
f. Only 3 children completed the treadmill test.

**Coding of Outcomes:**
Coding of comparison of study arm 1 versus study arm 2: (+) better, (–) worse (with reference to benefit for patient).

## Table 20. Target Hb Levels in the HD-CKD and PD-CKD Populations

| Outcome | No. of Studies & Study Design | Total N of Patients | Methodological Quality of Studies | Consistency across Studies | Directness of the Evidence, including Applicability | Other Considerations | Summary of Findings: Quality of Evidence for Outcome | Summary of Findings: Qualitative Description of Effect of High vs. Low Hb Target | Summary of Findings: Importance of Outcome |
|---|---|---|---|---|---|---|---|---|---|
| All-Cause Mortality | 7 RCTs | 2,790 | No limitations [a] | Important inconsistencies [b] | Some uncertainty [c] | None | High for patients with CVD<br>Moderately high for others | No benefit and possible harm. The Besarab study had a composite outcome of time to death or fatal MI with 183 deaths and 19 MIs vs. 150 and 14 (Hazards ratio [95% CI] 1.3 [0.9-1.9]). Other studies (without large number of CVD patients) show no difference between arms. | High |
| Nonfatal CV Events | 4 RCTs | 2,104 | Some limitations [d] | No important inconsistencies | Direct | Not sparse [e] | Moderately high | No benefit and possible harm. The Parfrey study reported higher CVA rates in the high Hb group, 4% vs. 1% (P = 0.045), but did not show differences in other CV event rates. | High |
| LVH | 3 RCTs | 780 | No limitations | Important inconsistencies [f] | Direct | None | High | No consistent or statistically significant benefit. Partial correction of anemia leads to partial regression of LVH; full correction has no incremental benefit over partial correction of anemia. | Moderate |
| Hospitalizations | 2 RCTs | 1,649 | Some limitations | No important inconsistencies | Major uncertainty [g] | Sparse data | Low | No benefit. The Besarab study and Furuland study showed NS. | Moderate |
| QOL-Global Score, Generic Instrument | 4 RCTs | 466 | Some limitations [h] | Important inconsistencies [i] | Direct | None | Moderately high | Benefit. 2 of 2 studies showed improved Sickness Impact Profile with higher target. Trials using Facit Fatigue and Health Utilities Index showed no differences. Beserab study did not report global score but showed increase in physical function. | High |
| QOL-With Kidney-Specific Instruments | 4 RCTs | 1,113 | Some limitations | Important inconsistencies [i] | Direct | None | Moderately high | Likely some benefit. All studies based on KDQ or derivative. 3 of 4 showed fatigue better (with higher Hb) 1 study approached statistical significance P = 0.05. 3 of 3 showed depression better. 2 of 4 showed physical symptoms better. 2 of 3 showed relationships better. 0 of 3 showed frustration better. 1 study approached statistical significance P = 0.05. | High |
| Transfusion Requirement | 5 RCTs | 1,808 | Some limitations [j] | No important inconsistencies | Some uncertainty [k] | None | Moderately high | Benefit. Transfusion rates reduced by as little as 1/3 to essentially 0 in all studies in higher Hb arms, Differences were statistically significant. | High |

*(Continued)*

| Outcome | No. of Studies & Study Design | Total N of Patients | Methodological Quality of Studies | Consistency across Studies | Directness of the Evidence, including Applicability | Other Considerations | Summary of Findings: Quality of Evidence for Outcome | Summary of Findings: Qualitative Description of Effect of High vs. Low Hb Target | Summary of Findings: Importance of Outcome |
|---|---|---|---|---|---|---|---|---|---|
| Access Thrombosis | 6 RCTs | 1,977 | Some limitations [l] | No important inconsistencies | Some uncertainty [m] | None | Moderately high | Harm. Increased risk of clotting with approximately 10% higher rate of thrombosis. Rates of thrombosis were 39% vs. 29% in the Besarab study, 21% vs. 12% in CanEPO. Other studies showed no significant differences. | High |
| Other Thrombo-embolic Events | 1 RCT | 416 | Serious limitations [n] | N/A | Some uncertainity [o] | Sparse Data | Low | No benefit. No statistically significant difference. OR of total vascular events was 1.24 (56 events) vs. 1.0 (47 events) (p = 0.37). | Moderate or high |
| Seizures | 4 RCTs | 1,690 | No limitations [p] | No important inconsistencies | Direct | Sparse Data | Low | Likely no harm. No statistically significant difference in the 2 large studies. CanEPO provides breakdown of 3 seizures in ESA vs. 0 in Placebo arms, the Besarab study does not provide actual data, but reports NS. | Moderate |
| Blood Pressure Change | 12 RCTs [q] | 2,617 | Some limitations [r] | Important inconsistencies [s] | Major uncertainity [t] | No dose effect [u] | Moderately high | Potential harm. In studies looking at high vs. low Hb 2 studies showed significant increase in SBP/DBP and number of antihypertensive medications. In Foley study, this was only true for subgroup with LVH, not in subgroup with LVD. 2 low quality studies suggest increase in DBP with higher ESA or ΔHb >2.2 g/dL. In studies comparing ESA vs. Placebo (6 RCTs ) the majority showed significant increases in SBP/DBP or number of antihypertensive medications needed in patients treated with ESA. [v] | Moderate |
| Dialysis Adequacy | 4 RCTs | 1,999 | No limitations [w] | No important inconsistencies | Direct [x] | None | High | Potential harm. Lower Kt/V in HD-CKD patients assigned to target Hb >13, in 4 of 4 trials. | Moderate [y] |
| Other AEs | 7 RCTs | 1,568 | Serious limitations [z] | N/A [aa] | Major uncertainty [ab] | Sparse and imprecise data [z] | Very low | Likely no harm. There seemed to be no pattern of higher rates of additional AEs in the higher Hb arms. | N/A |
| **Balance of Benefit and Harm:** **Net Benefit at Hb ≥11 g/dL based on QOL; Uncertain Trade Off with Increasing Hb Levels, QOL Benefit may be offset by potential for harm** | | | | | | | **Quality of Overall Evidence:** **Moderately High** | | |

**Footnotes:**

a 4 Grade A, 2 Grade B and 1 Grade C studies.

b The largest study (the Besarab study) showed significantly higher mortality in the higher Hb group. This study was composed of the highest-risk patients for CVD (i.e., possible confounder). The remaining studies showed no statistically significant difference.

c The duration of 3 of 7 trials was <1 yr; unclear if this is long enough to measure mortality outcome.

d 3 Grade A, 1 Grade B and 1 Grade C studies. However, the 3 A studies comprise 93% of patients. Most studies were inadequately powered to study nonfatal CVD events (i.e., possible confounder). The Besarab study was adequately powered to assess CHF, but was stopped early.

p 2 Grade A studies with ~1,300 patients and 2 Grade B studies.

q These 12 RCTs are 11 adult, 1 child (n = 21), 3 of the 11 are based on ABPM (n = 87). Only 6 involve placebo arms, others are ESA vs. ESA.

r 4 Grade A, 4 Grade B and 3 Grade C studies.

s Majority of problems are linked to the wide variation in definitions and measurements with respect to casual vs. ABPM, mean of SBP vs. DBP, different definitions of being hypertensive (being on medications vs. specific cut-off), defining worsening BP as both increase in BP and or medication amount/dose.

t Reason: Unclear how this translates into clinical outcomes.

| Summary of Findings | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Outcome | No. of Studies & Study Design | Total N of Patients | Methodological Quality of Studies | Consistency across Studies | Directness of the Evidence, including Applicability | Other Considerations | Quality of Evidence for Outcome | Qualitative Description of Effect of High vs. Low Hb Target | Importance of Outcome |
| e | 5/5 studies report outcomes of angina, 4/5 nonfatal MI, 3/5 pulmonary edema or heart failure. | | | | | u | Restricted to looking at 6 studies involving high- vs. low-dose ESA. | | |
| f | The Foley study shows a trend towards smaller LVMI and less progression in LV dilation in high vs. low Hb. | | | | | v | In the Furuland study, a number of patients were not on ESA in the low Hb arm but data were not available to extract; and only the Abraham study, which reported on only blood pressure outcomes from 3 other multi-site trials, did not show a difference in BP between ESA vs. placebo groups. | | |
| g | Not primary outcome; unclear if reason for admission can be solely related to the Hb level. | | | | | | | | |
| h | 2 Grade A and 2 Grade C studies; some studies not blinded, heterogeneity of timing and follow-up. | | | | | w | 3 Grade A studies. | | |
| i | Different instruments. | | | | | x | Only issue here is use of URR as 'surrogate' for Kt/V in the Foley study. | | |
| j | Transfusions were not primary outcome. | | | | | y | From the HEMO study, it is relatively clear that even a statistically significant decrease in Kt/V is unlikely to affect mortality (presume spKt/V >~1.3 URR 66%). | | |
| k | No trial specified indications for transfusions. | | | | | z | Ascertainment of additional AEs was not consistently or prospectively performed. Reporting was not standardized. Only AEs that occurred during duration of RCTs were captured. | | |
| l | 3 Grade A, 1 Grade B and 2 Grade C studies; the Besarab study had 76% grafts. (Other studies not powered to show difference in access clotting.) | | | | | aa | Numbers too small. | | |
| m | Most studies do not mention prior history of graft or fistula, i.e., its inherent risk of clotting. | | | | | ab | Reported events included sick leave, infection events, hyperkalemia, gastrointestinal symptoms, or were unspecified. | | |
| n | Primary outcome had been physical activity, study stopped, retooled, further enrollment, then another round of enrollment before recruitment complete. | | | | | | | | |
| o | Multiple sites across many countries. Only 1 coordinator recorded and classified events centrally and likely did not do site visits. Strength was the consistent use of scoring system from the World Health Organization. | | | | | | | | |

tional trials and cross-sectional analyses of large medical databases, such as within-group analyses in RCTs, consistently show that higher achieved Hb values (including ≥12 g/dL) are associated with improved patient outcomes, including lower mortality, less frequent hospitalization, and less severe LVH. Conversely, distinct-target RCTs consistently show that patients assigned to a Hb value of 13 g /dL or greater show no discernable improvement in survival, hospitalization, or LVH compared with patients assigned to Hb targets less than 13 g/dL and may be prone to excess adverse cardiovascular events. The failure of observational associations to be confirmed by interventional trials renders use of observational evidence unsuitable to support the development of an intervention guideline statement.

The statement that *Hb level should be 11.0 g/dL or greater* incorporates evidence from Hb targets ranging from 6 to 16 g/dL (Table 12 through Table 21; Fig 15). RCTs conducted before 1998 are characterized by small study size, higher target Hb levels within the range of 10 to 13 g/dL, and a lower target Hb level that reflects assignment to placebo or no-treatment control. Trials conducted thereafter are characterized by larger study size, higher target Hb levels within the range of 12 to 16 g/dL, and lower target Hb levels between 9 and 12 g/dL. The lesser magnitude of between-group Hb level differences seen in more recent trials is associated with Hb baseline values that are greater than those of early trials and lower target Hb level ranges that are substantially greater than Hb levels previously seen in placebo or untreated controls. In addition, mean Hb levels achieved in more recent trials frequently are at or less than the lower limit of the higher target Hb level range.

Patients in the 19 RCTs reviewed to support the statement that *Hb level should be 11.0 g/d or greater* clearly are representative of the anemic patients with CKD that the statement intends to address. Ten RCTs enrolled patients with HD-CKD, 1 enrolled patients with PD-CKD, 2 enrolled patients with both HD and PD-CKD (Tables 12 to 14), and 9 enrolled patients with ND-CKD (Tables 15 and 16). However, the preponderance of evidence (and thus the greatest strength of evidence) lies in the HD-CKD patient group. Although sample size and thus power,

**Table 21. Target Hb Levels in the ND-CKD Population**

| Outcome | No. of Studies & Study Design | Total N of Patients | Methodological Quality of Studies | Consistency across Studies | Directness of the Evidence, including Applicability | Other Considerations | Summary of Findings: Quality of Evidence for Outcome | Summary of Findings: Qualitative Description of Effect Size | Summary of Findings: Importance of Outcome |
|---|---|---|---|---|---|---|---|---|---|
| All-Cause Mortality | 5 RCTs | 336 | Some limitations [a] | No important inconsistencies | Some uncertainty [b] | Sparse data [c] | Very low | Unable to assess benefit or harm with any certainty | High |
| Nonfatal CV Events | 3 RCTs | 249 | Some limitations [d] | No important inconsistencies [b] | Some uncertainty [e] | Sparse data [c] | Very low | Unable to assess benefit or harm with any certainty | High |
| LVH | 2 RCTs | 307 | No limitations | No important inconsistencies | No major uncertainties | None | High | No statistically significant benefit. Difference between arms is not statistically significant. However, a trend toward LV growth in those maintained at the lower Hct. | Moderate |
| QOL | 2 RCTs | 238 | Some limitations [f] | N/A [g] | Some uncertainties [h] | Sparse data | Low | Likely some benefit. One study (achieved Hb 12.1 vs. 10.8 g/dL*) showed no improvement in QOL with early ESA intervention. A second study (achieved Hb 10.5 vs. 8.6 g/dL*) showed statistical improvement in the energy subscale, no overall score was provided. | High |
| Transfusion Requirement | 1 RCT | 83 | Major limitations [i] | N/A[j] | Some uncertainty [k] | Sparse data | Very low | Unable to assess benefit or harm with any certainty.There were more transfusions in the control arm (23%) than in the ESA arm (9%) but this difference was not statistically significant. | Moderate |
| Kidney Disease Progression | 9 RCTs | 502 | Some to major limitations [l] | Important inconsistencies [m] | Some uncertainty [n] | None | Low | Unable to assess benefit or harm with any certainty. The larger studies failed to show worsening of the rate of kidney disease progression in the ESA-treated arms. However, 2 very small studies suggested that dialysis started earlier in the occasional patient treated with ESA, but no statistics were given. The 2 largest, 1 study showed statistically significant prolonged renal survival in the ESA treated group which was larger in the subgroup without diabetes than in the group with diabetes. | High |
| Seizures | 3 RCTs | 39 | Major limitations [o] | N/A [j] | Some uncertainty [p] | Sparse data | Very low | Likely no harm. 0 vs. 2 individuals* in all studies noting seizures. | Moderate |
| Blood Pressure Change | 7 RCTs | 469 | Major limitations [q] | Some inconsistencies [r] | Some uncertainty [s] | None | Low | Potential harm. Studies either showed no significant change in BP with ESA treatment or there was a statistically insignificant trend towards patients who received ESA needing more antihypertensive management. | Moderate |
| **Balance of Benefit and Harm:** Net Benefit at Hb ≥11 g/dL based on QOL; Uncertain Trade Off with Increasing Hb Levels, QOL Benefit May Be Offset by Potential for Harm | | | | | | | **Quality of Overall Evidence:** Low | | |

**Footnotes:**
* ESA High vs. ESA Low or Treatment vs. Placebo/Control
a. 2 Grade A, 2 Grade B and 1 Grade studies.
b. Results are probably not generalizable as mortality was not a primary endpoint; mortality was not attributed to intervention in any of the studies.
c. Lack of adequately powered studies to evaluate the outcome.
d. 2 Grade A 1 Grade B studies.
e. Results are probably not generalizable since CV events were secondary endpoints; in none of the RCTs was morbidity attributed to intervention.
f. 1 Grade A study (with a statistically significant, but perhaps not clinically relevant, separation of Hb levels between arms) and 1 Grade B study.
g. Difference scales/tests used to asses QOL parameters.
h. QOL was a primary endpoint of only 1 study.
i. Trigger or threshold for transfusions were not defined.
j. Unable to assess due to 1 of the following: only 1 study, few studies of poor quality, studies with few subjects or no studies with the outcome ascertained as the primary outcome. Refer to Quality and Directness grades.
k. Secondary endpoint.
l. 3 Grade A, 2 Grade B and 4 Grade C studies.
m. Inconsistency in the statistical significance of effect..
n. BP and diet tightly controlled in some of the studies.
o. 2 studies of low quality and short duration to measure outcome.
p. Seizures were not primary or secondary outcomes of the studies.
q. 3 Grade A, 1 Grade B and 3 Grade C studies.
r. The importance of the inconsistencies is difficult to assess given poor quality of reporting.
s. Different outcome measures used with variable and uncertain clinical relevance, inconsistent reporting on BP as an outcome.

effect size, and strength of evidence generally are lower in patients with ND-CKD than patients with HD-CKD or PD-CKD, the direction of effect for key outcomes appears to be the same. Accordingly, the guideline statement is designed to address all anemic patients with CKD regardless of the presence, absence, or mode of dialysis therapy.

Endpoints measured to support the statement that *Target Hb levels should be maintained at greater than 11 g/dL* reflect key clinical outcomes important to patients. Measured outcomes include all-cause mortality, nonfatal cardiovascular events, LVH, hospitalization, QOL, transfusion requirement, access thrombosis, other thromboembolic events, seizure, blood pressure change, dialysis adequacy in patients with HD-CKD, and kidney disease progression in patients with ND-CKD (Table 12 and 16). Accordingly, the Work Group rated the importance of these outcomes as high or moderately high (Table 20 and Table 21).

Most distinct-target RCTs clearly have inadequate power to compare AE rates between patients in lower and higher Hb target groups for the key safety outcomes, mortality, MI, and cerebrovascular events (Table 12 and 16). There are 2 exceptions. In patients with HD-CKD with CVD, patients assigned to a Hb target level of 14 g/dL showed increased risk for death or MI compared with patients assigned to an Hb level of 10 g/dL,[108] a finding that did not reach significance (relative risk [RR], 1.3; 95% CI, 0.9 to 1.9). However, safety concerns prompted early study termination. In a second trial of patients with HD-CKD without symptomatic heart disease or left ventricular dilation, patients assigned to a Hb target of 13.5 to 14.5 g/dL showed a greater rate of cerebrovascular events than those assigned to an Hb target range of 9.5 to 11.5 g/dL ($P$ = 0.045).[109]

The risk for vascular access thrombosis in patients with HD-CKD likely increases as the target Hb level increases, over a wide range of potential Hb level targets. Patients assigned to Hb targets of either 9.5 to 11 or 11.5 to 13 g/dL show increased access thrombosis compared with placebo-treated controls,[49] as do patients assigned to a Hb target of 14 g/dL compared with those assigned to a target of 10 g/dL.[108] Native arteriovenous fistulae fare no better than arteriovenous grafts.[49,108]

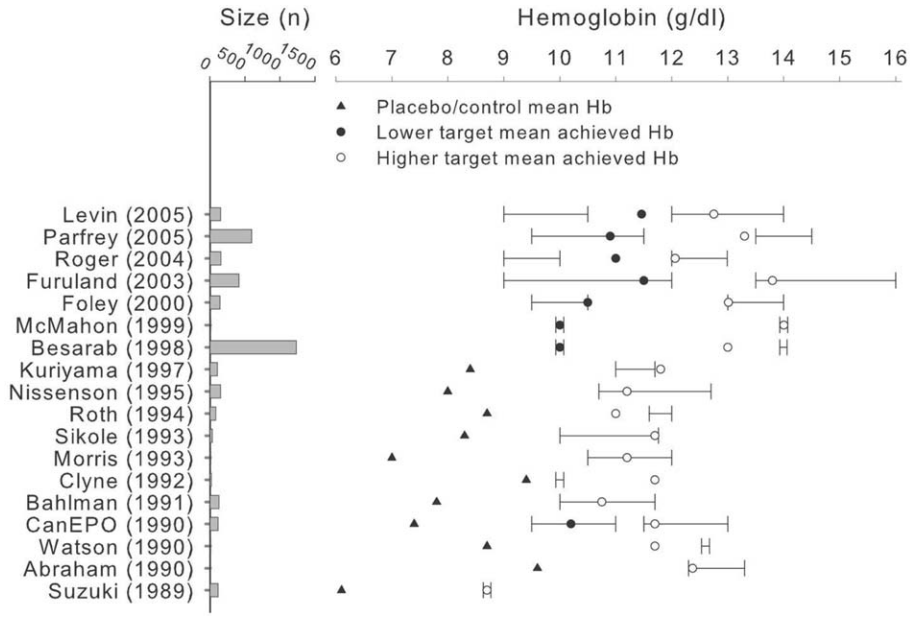


**Fig 15. Target and achieved Hb levels in 18 RCTs comparing higher against lower (or placebo/control) Hb targets for ESA therapy. Whiskers denote the assigned (intent-to-treat) Hb target, data points denote achieved Hb level (see legend). Not shown is Lim 1989, Berns 1999, Abraham 1991 (see Tables 12 and 14). For literature citations, see Table 12 through Table 21.**

Substantial blood pressure increases requiring intervention are seen in ESA-treated patients regardless of Hb target compared with those assigned to placebo or no-ESA control groups. Increased antihypertensive use to achieve equivalent blood pressure also has been seen in patients assigned to higher Hb targets compared with lower Hb targets.[109,110] However, use of placebo and no-treatment control groups is confined to early trials in which patients entered with low baseline Hb levels and, with treatment, showed large relative differences between achieved Hb target (upper or lower) and baseline Hb levels (Fig 16). Blood pressure effects between upper and lower Hb targets appear less prominent in recent trials compared with earlier trials; however, it is unclear whether this difference is caused by relatively high baseline Hb levels, small differences between baseline and either upper and lower target achieved Hb levels, small differences between upper and lower achieved target levels, or differences in patient selection between early and more recent trials.

Hospitalizations and seizures appear not to be affected by target Hb level in patients with either HD-CKD, PD-CKD, or ND-CKD (Table 20 and Table 21). Dialysis adequacy is lower and transfusions less frequent among patients with HD-CKD in higher-target compared to lower-target treatment groups (Table 20).

In patients with ND-CKD, the effect of Hb target on progression of kidney disease is unclear. Eight RCTs enrolling more than 500 total patients yielded inconsistent results. Individual trials showed either prolongation of kidney survival, acceleration of progression to kidney failure, or no effect, but many of the trials were underpowered to detect potentially relevant effects in either direction. Because of this limitation, the unavoidable use of compound interventions (early versus late plus lower versus higher Hb targets), and the lack of consistency in results, the Work Group concluded that considerations of kidney disease progression currently should not influence the determination of Hb targets in patients with ND-CKD.

QOL outcomes—particularly those reflecting vitality, fatigue, and physical function—show a consistent positive relationship to level of Hb target that appears to be continuous within the examined Hb level range of 6 to 16 g/dL. Patients report greater vitality, less fatigue, less depression, and improved physical symptoms at higher compared with lower Hb targets. These

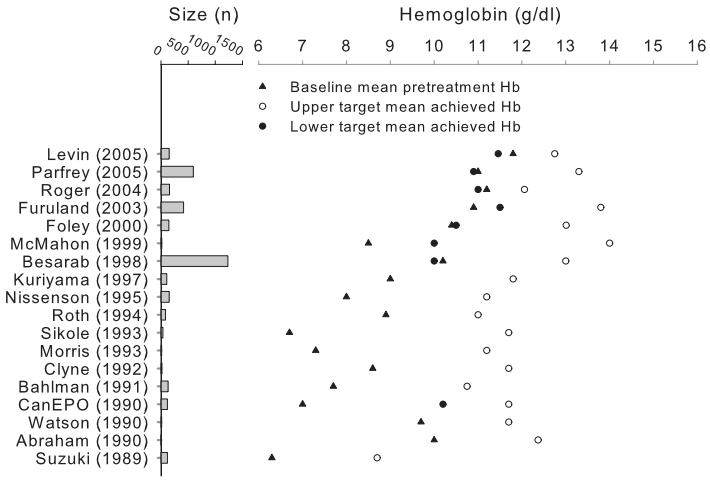


**Fig 16. Baseline mean pretreatment Hb levels compared with achieved mean Hb levels in the upper and lower target. Results for achieved lower target Hb levels are not shown for placebo/control groups. Data for Lim 1989 (4 target groups, n = 14 total), Berns 1999 (n = 24), and Kleinman 1989 (n = 14) not shown. In recent trials, baseline Hb level approaches or exceeds the achieved target Hb level of early trials, and differences between baseline and target upper achieved Hb levels are relatively small. For literature citations, see Table 20 and Table 21.**

results appear to be instrument dependent because differences are more readily discernable with testing instruments specific for CKD. Other dimensions of QOL show less consistent results regardless of the instrument used. Although effect size of QOL outcomes and the quality of evidence are lower in ND-CKD compared with HD-CKD and PD-CKD trials, the direction of effect is similar in all populations tested. The Work Group rated QOL as highly important to patients (Table 20 and Table 21).

In developing the statement *Hb level should be 11.0 g/dL or greater*, the Work Group concluded that—when comparing higher with lower Hb targets—QOL is a sufficient and, apparently, the sole determinant of treatment benefit. However, both the design of the RCTs supporting that conclusion and the continuous nature of the relationship between QOL and Hb level pose challenges to translating evidence into a guideline statement. Hb targets in RCTs are designed to ensure separation of treatment results in higher Hb target groups compared with lower Hb target groups to maximize the possibility that between-group treatment effects will be detected. These targets, whether represented as discrete Hb values (eg, 10.0 versus 14.0 g/dL[108]) or a range of Hb values (eg, 9.0 to 10.0 versus 12.0 to 13.0 g/dL[38]), (1) were not intended to serve as Hb targets for anemia management in clinical practice, (2) are ill suited to the purpose of measuring clinical performance, and (3) if adopted as a CPG, would discourage flexibility in meeting the needs of individual patients. Moreover, because the relationship between QOL and Hb level that emerges from RCT results is continuous, there is no specific threshold Hb value to distinguish between the presence and absence of benefit.

The Work Group considered, but rejected, identifying a discrete Hb value (eg, 11.0 g/dL) as a Hb target. A discrete target Hb level affords clarity and simplicity, but is almost universally impossible to achieve, renders implementation as a performance measure difficult, and discourages flexibility in using tradeoff decision making to meet the needs and preferences of individual patients.

Similarly, the Work Group considered, but rejected, identifying a target Hb level bounded by narrow upper and lower values (eg, 11.0 to 12.0 g/dL). Such a target affords neither clarity nor simplicity, is possible to achieve in only a minority of patients,[111-113] discourages flexibility in managing individual patients, and likely promotes cycling of Hb results greater than and less than the target.[114]

The Work Group chose to define a broad therapeutic range of Hb levels bounded by a discrete lower threshold above which Hb level should be maintained and a upper threshold

above which Hb should not be *routinely* maintained. This approach makes clear to the practitioner that no patient should be maintained *intentionally* at less than the lower threshold, and patients should not be routinely maintained at greater than the upper threshold. We chose 11.0 g/dL as the lower Hb level threshold. Hb values at or near 11.0 g/dL comprise an approximate watershed, defining the upper Hb targets of early RCTs and the lower targets of more recent trials (Fig 15). Thus, evidence to support the lower limit of Hb statement draws on the full range of RCTs available and the full range of Hb targets examined. This evidence supports the conclusion that patients treated to a Hb target greater than 11.0 g/dL likely will experience measurable QOL benefits with little or no increase in AEs compared with treatment at lower Hb levels.

Hb values greater than 11 g/dL are readily achievable. Greater than 80% of prevalent patients with HD-CKD in the United States currently demonstrate Hb levels of 11.0 g/dL or greater.[28] Among patients with a Hb level less than 11.0 g/dL, greater than 99.6% achieve Hb values of 11.0 g/dL or greater within 6 months when prescribed sufficient ESA. Thus, the guideline as stated can be implemented readily in clinical practice and provides a rational foundation for developing clinical performance measures for anemia management.

*In the opinion of the Work Group, there is insufficient evidence to recommend routinely maintaining Hb levels at 13.0 g/dL or greater in ESA-treated patients.*

Evidence reviewed in the foregoing rationale supports the conclusion that QOL benefits associated with treating to a higher Hb target extend throughout the full range of Hb targets examined to date, spanning 6 to 16 g/dL. However, the same evidence suggests that treating to Hb targets greater than 13 g/dL may increase the risk for serious AEs. The only trial that had sufficient power to examine safety assigned patients to a target Hb level of 14.0 g/dL in the higher-target treatment arms[108] and compared outcomes with those seen in patients assigned to a lower Hb target (10.0 g/dL). That trial was discontinued for safety concerns. In a second trial, patients assigned to a higher Hb target (13.5 to 14.5 g/dL) showed an increased incidence of cerebrovascular AEs compared with those assigned to a lower target (9.5 to 11.5 g/dL).[109] Two additional trials compared the efficacy and safety of Hb targets in patients with ND-CKD, Cardiovascular Risk Reduction by Early Anemia Treatment With Epoetin Beta Trial (CREATE; Hb level of 10.5 to 11.5 versus 13.0 to 15.0 g/dL)[115] and Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR; Hb level of 11.3 versus 13.5 g/dL).[115A] The CREATE trial has been completed, whereas the CHOIR trial has been terminated early by decision of the trial safety committee. Results from either trial are not published at the time of this writing.

In short, efforts to gain QOL benefits by treating to Hb targets of 13 g/dL or greater are countered by increased risk for life-threatening or disabling AEs. The statement that *There is insufficient evidence to recommend routinely maintaining Hb levels at 13.0 g/dL or greater* recognizes the concern that, for most patients, the known risks outweigh the known benefits of treating to higher Hb level. The phrase *insufficient evidence* reflects the finding that published results from comparative trials large enough to examine safety are relatively limited.

Moreover, the word *routinely* reflects the crucial limitations of currently available evidence and the need for further investigation. For example, no clinical trial conducted to date has examined target Hb safety and efficacy in selective subgroups that may especially benefit from higher Hb targets, including, for example, patients who live at high altitude, are employed, have pulmonary disease, have high levels of physical performance, or undergo daily or nocturnal HD. In the absence of information in these and other potential subgroups, medical decision making requires weighing known risks and benefits in mixed-study populations against unknown risks and unknown benefits in individual patients.

The statement *Routinely maintaining patients at Hb levels of 13 g/dL or greater* makes it clear that the recommended upper limit of Hb level applies only to patients considered for maintaining a Hb level at 13 g/dL or greater as a treatment target, not patients for whom Hb level is likely to transiently equal or exceed 13 g/dL while undergoing treatment for a lower Hb target, and not patients who do not require ESA therapy. Given the biological variation in Hb

levels in patients with HD-CKD, if the intent of treatment is to maintain Hb levels at 11.0 g/dL or greater, a sizeable fraction of patients will necessarily show Hb values transiently at 13 g/dL or greater. Judicious ESA dose adjustments appear sufficient to correct Hb values above intended targets within 3 to 6 months.[112]

## LIMITATIONS

### *Limits of Available RCTs*

The strength of an RCT is to study a specific question by studying the efficacy of an intervention on specific outcomes in a well-defined population. Findings from RCTs thus are often limited in their generalizability to diverse populations or to questions related to effectiveness of combinations of interventions on combinations of patient outcomes. These latter questions are what guidelines attempt to address. For example, consider a hypothetical study designed to compare the effect of 3 Hb treatment targets: Hb level less than 9 g/dL, Hb level of 9 to 12 g/dL, and Hb level greater than 12 g/dL. Patient populations should be separated into patients with or without CVD and: (1) ND-CKD, (2) HD-CKD, (3) PD-CKD, or (4) transplant-associated CKD. Each discreet Hb target, CVD status, and each CKD category deserves scrutiny. However, this is unfeasible: the hypothetical RCT would collapse under the weight of a $3 \times 2 \times 4$ (24-group) study design.

Imagine instead constructing a 24-cell matrix to represent all possible combinations of Hb targets, CVD status, and CKD categories that we wish to examine. If we added all the results from all available RCTs to the specific cells addressed by the available RCTs, we would have to leave the vast majority of cells empty at this writing. Given the small number of RCTs and the small size of most of the available RCTs, and given the potential differences between target populations, filling in empty cells by extending results from the few completed cells seems unwarranted and likely to involve substantial error.

Another critical limitation of the evidence, as discussed, is the lack of information about the comparative safety and efficacy of lower versus higher Hb targets in selected subgroups of patients that may especially benefit from higher Hb targets.

### *QOL/QOL Trade-Off*

QOL, like quantity of life, is a hard patient outcome. Available evidence confirms that setting Hb targets for individual patients requires consideration of the potential trade-off between QOL and survival, MI, cerebrovascular event, or access thrombosis. However, although we know that risk assessment varies widely by culture, personal values, level of education, and level of medical literacy, we lack information on how to assist patients with CKD to interpret risk, judge risk-benefit trade-offs, and express informed preferences. Nevertheless, in everyday medical decision making, it is important to incorporate informed patient preference.[116]

### *Differences in Treatment Strategies Used To Achieve Defined Hb Targets*

The duration of anemia before initiating ESA therapy and the size and rate of Hb level correction each plausibly contributes to risk, benefit, or both in anemia therapy. Information on each would be directly helpful to clinicians.

Similarly, it is possible that the risks and benefits associated with a target Hb level depend in part on which therapeutic agents were used in the treatment arm. All available hard-outcome trials to date have used both ESAs and iron agents together in patients assigned to both treatment and control arms. No trial using ESA alone, iron alone, or noniron adjuvants alone has been adequately designed and powered to confirm that similar Hb targets afford similar risks and benefits regardless of how they are attained. The possibility that each potential class of agents, including ESAs, oral iron, parenteral iron, and non-iron adjuvants, shows differing patient outcomes for equivalent Hb outcomes has not been explored.

# CPR 3.1. USING ESAs

ESAs are critical components in managing the anemia of CKD. Available ESAs are each effective in achieving and maintaining target Hb levels. Aspects of administration may differ between short-acting and long-acting agents.

**3.1.1 Frequency of Hb monitoring:**

**3.1.1.1 In the opinion of the Work Group, the frequency of Hb monitoring in patients treated with ESAs should be at least monthly.**

**3.1.2 ESA dosing:**

**3.1.2.1 In the opinion of the Work Group, the initial ESA dose and ESA dose adjustments should be determined by the patient's Hb level, the target Hb level, the observed rate of increase in Hb level, and clinical circumstances.**

**3.1.2.2 In the opinion of the Work Group, ESA doses should be decreased, but not necessarily withheld, when a downward adjustment of Hb level is needed.**

**3.1.2.3 In the opinion of the Work Group, scheduled ESA doses that have been missed should be replaced at the earliest possible opportunity.**

**3.1.2.4 In the opinion of the Work Group, ESA administration in ESA-dependent patients should continue during hospitalization.**

**3.1.2.5 In the opinion of the Work Group, hypertension, vascular access occlusion, inadequate dialysis, history of seizures, or compromised nutritional status are not contraindications to ESA therapy.**

**3.1.3 Route of administration:**

**3.1.3.1 In the opinion of the Work Group, the route of ESA administration should be determined by the CKD stage, treatment setting, efficacy, safety, and class of ESA used.**

**3.1.3.2 In the opinion of the Work Group, convenience favors subcutaneous (SC) administration in non–HD-CKD patients.**

**3.1.3.3 In the opinion of the Work Group, convenience favors intravenous (IV) administration in HD-CKD patients.**

**3.1.4 Frequency of administration:**

**3.1.4.1 In the opinion of the Work Group, frequency of administration should be determined by the CKD stage, treatment setting, efficacy considerations, and class of ESA.**

**3.1.4.2 In the opinion of the Work Group, convenience favors less frequent administration, particularly in non–HD-CKD patients.**

## BACKGROUND

The decision to start ESA therapy in a patient with CKD-associated anemia invokes an additional series of decisions that must be made before the first dose is administered. Each of the following issues must be considered before moving forward: choosing an ESA, an initial ESA dose, and the route and frequency of ESA administration; planning a Hb level monitoring schedule; predicting a desired rate of increase in Hb level; and anticipating ESA dose adjustments for Hb results, AEs, or intercurrent hospitalizations. Making informed decisions requires understanding the method of action of ESAs, then selecting those which best fit the patient, the patient-care setting, and the constraints of the health care delivery system from the range of choices that are known to be safe and effective.

## RATIONALE

### *Definitions*

The term ESA applies to all agents that augment erythropoiesis through direct or indirect

action on the erythropoietin receptor. Currently available ESAs include epoetin alfa, epoetin beta, and darbepoetin. Epoetin alfa and beta have been designed to resemble closely the endogenous molecule and have similar pharmacokinetics. They are considered "short-acting" in comparison to darbepoetin, a second-generation molecule with a prolonged half-life, which is considered "long-acting."

### *Frequency of Hb Monitoring*

The statement *The frequency of Hb monitoring in patients treated with ESA should be at least monthly* is intended to provide sufficient surveillance information to assist in achieving and maintaining target Hb levels safely and expeditiously during ESA therapy. This recommendation, which fits common practice, follows a chain of reasoning. The minimum interval between ESA dose adjustments is 2 weeks because the effect of most dose changes will not be seen within a shorter interval. Consideration of an ESA dose adjustment is based on the next projected Hb level. Because the accuracy of projection (extrapolation) increases with the number of contributing data points, the frequency of Hb monitoring is likely to be an important determinant of the accuracy of ESA dose adjustment. Evidence to support this line of reasoning is indirect. Several RCTs have randomized HD patients with target-range Hb levels to a change in frequency of ESA administration, a change in ESA class, or both. RCTs that have monitored Hb values weekly and adjusted ESA doses as frequently as every 2 weeks have achieved stable Hb levels early after randomization.[136-138] A single RCT that monitored Hb levels and considered ESA dose adjustment monthly required 6 to 9 months to stabilize Hb levels after randomization,[139] but mean Hb level remained within the target range for that trial.

Within the recommended ranges for monitoring and dose adjustment, unstable Hb level, out-of-target Hb level, and HD favor shorter intervals, whereas stable Hb level, within-target Hb level, PD, ND-CKD, and minimizing laboratory resource utilization favor longer intervals. The frequency of ESA dose adjustment is unaffected by length of action: during an 8-week period, given Hb monitoring weekly, short-acting ESA thrice weekly or long-acting ESA once weekly, and consideration for dose adjustment every 2 weeks, 44% to 49% of patients will actually require dose adjustment.[138]

### *ESA Dosing*

*The initial ESA dose and ESA dose adjustments should be determined by the patient's Hb level, the target Hb level, the observed rate of increase in Hb level, and clinical circumstances.*

This statement aims to guide medical decision making so that the initial rate of increase in Hb levels is in keeping with the patient's current status, the treatment setting, and the patient's need for anemia treatment. In general, the objective of initial ESA therapy is a rate of increase in Hb levels of 1 to 2 g/dL per month. Evidence for the safety of initial ESA therapy derives principally from interventional trials in patients not previously treated with ESAs. In patients with CKD-associated anemia and initial Hb levels less than target range, these trials have shown the mean initial rate of Hb level increase to be in the range of 0.7 to 2.5 g/dL in the first 4 weeks. The rate of increase varies greatly and depends in part on the patient population, initial dose, dosing frequency, and route of administration (Table 22). Hypertension and seizures were noted in the first 3 months after initiating therapy in severely anemic patients, but it is unclear whether these events occurred within the first 4 weeks and whether they were related to the rate of increase in Hb levels.

In general, ESA dose adjustments were not made in the first 4 weeks of trials for which results are available. The frequency of ESA dose adjustment thereafter should be determined by the rate of increase in Hb levels during initial ESA therapy, the stability of Hb levels during maintenance ESA therapy, and the frequency of Hb testing. The minimum interval between ESA dose adjustments in the outpatient setting generally is 2 weeks because the effect of most dose changes will not be seen within a shorter interval.

*ESA doses should be decreased, but not necessarily held, when a downward adjustment of Hb level is needed.* Withholding ESA doses, particularly for long periods, may lead to a delayed decrease in Hb levels to less than target range. Such a decrease may initiate

**Table 22. Anemia Management Protocol Information for Initial Anemia Management Used in ESA RCTs**

| Author, Year | N | CKD Class | Baseline* | | | | | Initial ESA dose | Outcome | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Hb (g/dL) | Oral Iron | IV Iron | ESA Frequency | ESA Route | | Adjustment: Acute | | Mean Rise of Hb (g/dL) in 1st 4 weeks | AEs |
| | | | | | | | | | Upward | Downward | | |
| Eschbach, 1989 [144] | 201<br>35 | HD | 7.4<br>8.1 | | As needed | TIW | IV | Epoetin<br>150<br>300 | None | None | 1.5<br>2.5 | Seizure in 10 patients in 1st 3 mo, did not distinguish by month, rate of Hb rise or ESA dose |
| Eschbach, 1989 [145] | 4<br>4 | 4-5<br>ND | 8.9 | | | TIWk | SC<br>IV | Epoetin<br>100<br>150 | None | None | 2.5<br>1.3 | None |
| Nissenson, 1995 [123] | 78 | PD | 7.9 | 86% | As needed | TIW | SC | Epoetin<br>4,000 | None | None | 1.8 | Worsening hypertension in 1st 12 wk, no specific information on 1st 4 wk |
| Locatelli, 2001 [146] | 37<br>129 | 4-5<br>ND | 9.8<br>9.2 | | As needed for low indices | QOW<br>BIW | SC | Darbepoetin<br>0.45 µg/kg<br>Epoetin<br>50 IU/kg | 25% of starting dose | 25% of starting dose | 1.0<br>1.1 | |
| Toto, 2004 [147] | 463 | 3-5<br>ND | 9.8 | 60% | 14% | QOW | SC | Darbepoetin<br>0.75 µg/kg | Next dose size | Next dose size | 0.7 | Next dose size |
| Roth, 1994 [81] | 43 | 4-5<br>ND | 7.8 | As needed | As needed | TIW | SC | 50 IU/kg | 75 IU/kg increments | No info | 1.6 | |
| Nissenson, 1995 [123] | 78 | PD | 7.4 | 86% | 23% | TIW | SC | 4,000 IU | None | None | 1.8 | |

**Footnotes:**
Studies selected included only RCTs; only patients previously naive to ESA; with data available on Hb (or Hct) at 4 (or at both 3 and 5 wk), compared to baseline.

**Coding of Comparison of Outcomes:**
If Hct reported, Hb was obtained by dividing by 3.3. If 4-wk value was not reported, result was interpolated.

periodic cycling of Hb levels at greater than and less than the target Hb range.[114] This finding is in keeping with the mechanism of action of ESA in preventing apoptotic death of CFU-Es and early erythroblasts. Should ESA doses be withheld in an ESA-dependent patient, a prolonged loss of erythropoietic precursors may result. Accordingly, the Work Group recommends that ESA doses not be withheld routinely for Hb levels greater than target range, hospitalization, poorly controlled hypertension, or vascular access occlusion.

The statement *Scheduled ESA doses that have been missed should be replaced at the earliest possible opportunity* reflects the concern that missed doses of ESA, like held doses, may lead to a delayed decrease in Hb levels to less than target range. This is illustrated most clearly in patients who receive ESA dosing every 2 to 4 weeks, but the principle applies to all patients undergoing ESA therapy.

Similarly, the statement *Hypertension, vascular access occlusion, inadequate dialysis, history of seizures, or compromised nutritional status are not contraindications to ESA therapy* aims to discourage the practice of withholding ESA therapy in the presence of conditions potentially linked to anemia treatment. If these disorders arise in the course of anemia therapy with ESA, they should be treated appropriately with specific measures. There is no evidence that withholding ESA therapy improves patient outcomes in these settings.

### *Route of Administration*

*The route of administration should be determined by the CKD stage, treatment setting, efficacy considerations, and the class of ESA used.* Among patients with HD-CKD, either SC or IV administration is possible. In the outpatient setting, SC administration is the only routinely feasible route of administration for patients with PD-CKD and ND-CKD. Among patients with HD-CKD, either SC or IV administration is feasible, but the risk for pure red cell aplasia (PRCA) associated with SC administration, albeit small, recently prompted the US Food and Drug Administration (FDA) to recommend the IV route. The relationship between SC ESA administration and risk for PRCA experienced outside the United States is discussed elsewhere (Guideline 3.5).

Among short-acting ESAs, efficacy of SC administration in patients with HD-CKD is superior to that of IV administration. Although many trials have achieved similar results, the findings of a single large multicenter RCT are sufficient to establish the strength of evidence for this guideline statement.[140] In this trial, patients with HD-CKD were eligible for randomization only if they were currently receiving epoetin alfa and their Hct was within the target range. Upon randomization (from SC or IV to IV or SC), ESA

doses were first decreased to allow Hb levels to decrease to less than target range. Doses then were titrated upward to again achieve target Hct levels, then were adjusted to maintain Hct in the target range during a 26-week maintenance phase. Among patients who completed the trial, those assigned to SC administration showed 27% lower ESA doses than those assigned to IV administration. Mean achieved Hcts did not differ between groups. Of the patients who, by assignment, switched from IV to SC administration, 58% showed a decrease in ESA dose and 23% showed an increase; among their counterparts who switched from SC to IV administration, the corresponding proportions were 28% and 49%, respectively. In short, SC administration of short-acting ESAs is associated with an approximately 30% decrease in ESA dose for the same target Hb outcome. However, not all patients show a dose decrease after conversion from IV to SC, and some will show a dose increase.

Among long-acting agents, efficacy of SC compared with IV administration appears to be equivalent at examined dosing frequencies.[137,141]

### *Frequency of Administration*

*Frequency of administration should be determined by the CKD treatment setting and the class of ESA.* Selecting frequency of ESA administration may require a choice between maximum efficacy and optimum convenience and comfort. Maximum efficacy occurs within dosing intervals that are ESA class specific. For example, in patients with HD-CKD receiving SC short-acting ESA therapy, ESA efficacy decreases when the dosing is extended from thrice-weekly to once-weekly administration.[139] When every-2-week administration of long-acting ESAs is extended to every 4 weeks, efficacy either remains stable[142] or decreases incrementally.[143]

## LIMITATIONS

In practice, the use of ESAs is subject to wide variability that reflects broad differences in practice setting, patient preference, and reimbursement constraints. The definition of best practice therefore should reflect both available evidence and prevailing conditions, preferences, and priorities. The evidence base for CPRs on the use of ESAs requires information generated from quality improvement programs and anemia management protocols that examine multiple interventions and explicitly state underlying goals and assumptions.

# CPG AND CPR 3.2. USING IRON AGENTS

Anemia therapy in patients with CKD requires effective use of iron agents, guided by appropriate testing of iron status. Efficacy of iron therapy appears not to be limited to patients with evidence of iron deficiency. (See Guideline 1.2 for diagnosis of iron deficiency.) Thus, the goals of iron therapy are to avoid storage iron depletion, prevent iron-deficient erythropoiesis, and achieve and maintain target Hb levels.

**3.2.1 Frequency of iron status tests:**
**In the opinion of the Work Group, iron status tests should be performed as follows:**
**3.2.1.1 Every month during initial ESA treatment.**
**3.2.1.2 At least every 3 months during stable ESA treatment or in patients with HD-CKD not treated with an ESA.**

**3.2.2 Interpretation of iron status tests:**
**In the opinion of the Work Group, results of iron status tests, Hb, and ESA dose should be interpreted together to guide iron therapy.**

**3.2.3 Targets of iron therapy:**
**In the opinion of the Work Group, sufficient iron should be administered to generally maintain the following indices of iron status during ESA treatment:**
**3.2.3.1 HD-CKD:**
- **Serum ferritin >200 ng/mL**

***AND***

- **TSAT >20%, or CHr >29 pg/cell.**

**3.2.3.2 ND-CKD and PD-CKD:**
- **Serum ferritin >100 ng/mL**

***AND***

- **TSAT >20%.**

**3.2.4 Upper level of ferritin:**
**In the opinion of the Work Group, there is insufficient evidence to recommend routine administration of IV iron if serum ferritin level is greater than 500 ng/mL. When ferritin level is greater than 500 ng/mL, decisions regarding IV iron administration should weigh ESA responsiveness, Hb and TSAT level, and the patient's clinical status.**

**3.2.5 Route of administration:**
**3.2.5.1 The preferred route of administration is IV in patients with HD-CKD. (*STRONG RECOMMENDATION*)**
**3.2.5.2 In the opinion of the Work Group, the route of iron administration can be either IV or oral in patients with ND-CKD or PD-CKD.**

**3.2.6 Hypersensitivity reactions:**
**In the opinion of the Work Group, resuscitative medication and personnel trained to evaluate and resuscitate anaphylaxis should be available whenever a dose of iron dextran is administered.**

## BACKGROUND

The goal of iron therapy in a patient with anemia and CKD is to achieve and maintain a target-range Hb level. Iron agents may serve as primary therapy for selected patients (particularly those with ND-CKD) or as adjuvant therapy for those also undergoing treatment with an ESA. Administered as adjuvants to ESAs, iron agents prevent iron deficiency and serve to minimize the dose of ESA needed to achieve target-range Hb levels. Designing appropriate iron therapy for patients with CKD-associated anemia requires an understanding of the interpretation of iron status test results, the therapeutic significance of iron status levels, and the therapeutic and safety limits of iron administration. Selecting a route of administration, dose, and class of iron agent requires an understanding of the efficacy, safety, and tolerability of available iron therapeutics. The stage of CKD and treatment setting (HD-CKD and PD-CKD) deserve consideration not only for practical reasons, but also because the quantity, quality, and strength of evidence vary among patients with ND-CKD, HD-CKD, and PD-CKD.

## RATIONALE

### *Frequency of Iron Status Tests Should Be Every 1 to 3 Months*

The purpose of iron status testing is to either evaluate anemia or guide the use of iron agents to achieve and maintain targets of iron therapy during anemia management. Use and interpretation of iron status tests in the initial evaluation of anemia are described in Guideline 1.2.

Frequency of iron status testing during anemia management should be determined by the patient's Hb level relative to the target range and by the likelihood of blood loss. Initiation of ESA therapy, correction of a less-than-target Hb level during ongoing ESA therapy, bleeding, and surgical procedures each are likely to promote depletion of iron stores and thereby may call for increased frequency of iron status testing. Similarly, iron status testing is appropriate after treatment with a course of IV iron, to monitor safety and adequacy of therapy, and in a patient with hyporesponsiveness to ESA.

Clinical settings in which more frequent iron testing may be necessary include the following:

1. Initiation of ESA therapy
2. Correction of a less-than-target Hb level during ongoing ESA therapy
3. Recent bleeding
4. After surgery
5. After hospitalization
6. Monitoring response after a course of IV iron
7. Evaluation for ESA hyporesponse.

### *Interpretation of Iron Status Test Results Should Incorporate Hb and ESA Dose*

In a patient undergoing ESA therapy, interpretation of the results of iron status tests should incorporate consideration of the Hb level and ESA dose. Together, these results provide information important to medical decision making because they elucidate the status of both external iron balance (net loss or gain of iron) and internal iron balance (disposition of iron between stores and circulating red blood corpuscles). For example, a decreasing ferritin level in the presence of a stable or decreasing Hb level may signify external iron loss (GI bleeding or, in patients with HD-CKD, dialysis-associated blood loss). In this case, iron therapy may be indicated to replace iron deficits. Conversely, a decreasing ferritin level in the presence of an increasing Hb level signifies an internal shift in iron from stores to Hb, as would be expected in a patient responding to ESA therapy. If iron status remains within the target range, additional iron administration may not be required. If the Hb level is greater than the target range and is being corrected by decreasing the ESA dose, ferritin level may increase as the Hb level corrects. Again, no iron may be needed. Finally, an increase in ferritin level accompanied by a decrease in TSAT suggests inflammation-mediated reticuloendothelial blockade and may be accompanied by a decrease in Hb level and increase in ESA dose. Whether and to what extent iron administration is effective and safe in this setting remains unresolved.

In short, medical decision making in using iron agents—including initiation of iron therapy, choice of route of iron administration, and determination of dose and duration of iron therapy—should be guided by results of iron status tests taken together with Hb levels and ESA dose, combined with a trend analysis of how each has changed over time.

### *Targets of Iron Therapy*

In this section, we distinguish the therapeutic use of iron status tests from their diagnostic use. As diagnostic indices, iron status tests are helpful in determining the likelihood that iron deficiency is contributing to a low Hb level in patients with anemia and CKD (Guideline 1.2). In all patients with CKD, as in non-CKD patients, evidence of iron depletion and iron deficiency should prompt consideration of blood loss, and further evaluation may be needed (Guideline 1.2).

By contrast the statement *Targets of iron therapy* refers to results of iron status tests as treatment targets for the safe and effective use of iron agents. In patients receiving ESA therapy, iron status treatment targets serve to minimize the ESA doses required to maintain target-range Hb levels. In patients not receiving ESA therapy, iron status treatment targets serve to maximize the Hb level and minimize the need to initiate ESA therapy to achieve target-range Hb levels. Targets of iron therapy reflect the treat-to-target goals for the use of iron agents in patients with HD-CKD, ND-CKD, and PD-CKD with anemia.

**Table 23. RCTs for Ferritin and TSAT Targets in the HD-CKD Population**

| Author, Year | N | Follow-up (mo) | Applicability | Baseline | | | | Co-intervention | Description of Arms | Intervention | Target (Achieved) | Outcome Arm 1 vs. Arm 2 | | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Hb (g/dL) | ESA Dose | Ferritin (ng/mL) | TSAT (%) | | | | | Definition | Result | P-value | |
| Besarab, 2000 [148] | 23 | 6 | ↑↑ | 10.6 | 3,625 IU TIW | 285 | 24.6 | ESA adjusted to maintain baseline Hb | High TSAT (%) | IV iron dextran 100 mg for 4-6 HD sessions followed by 25-150 mg/wk | 30-50 (30.9-34.9) [a] | ESA dose | Arm 1 approximately 40% less than arm 2 at months 4-6 [b] | 0.004 | ● |
| | 19 | | | 10.5 | 3,782 IU TIW | 287 | 23.9 | | Low TSAT (%) | Weekly doses of IV iron dextran 25-150 mg/wk | 20-30 (24.5-27.6) | | | | |
| DeVita 2003 [149] | 19 | 5 | ↑↑ | 9.8 | 312 IU/kg/wk | 166 | nd | ESA adjusted to maintain Hb of 10.8-12 g/dL | High Ferritin (ng/mL) | IV iron dextran if below target 100 mg for 10 HD sessions | 400 (469) | Mean decrease in ESA dose | 154 vs. 31 IU/kg/wk | <0.001 | ◎ |
| | 17 | | | 10.2 | 250 IU/kg/wk | 204 | nd | | Low Ferritin (ng/mL) | | 200 (299) | | | | |

Footnotes:
a. Range of mean TSAT for months 4-6.
b. Arm 1: 52% vs. Arm 2: 21% had at least a 20% reduction in ESA dose (P <0.05).

*Iron Targets in Patients With HD-CKD*

Evidence to support the development of an iron target guideline in patients with HD-CKD is drawn from tissue iron studies (semiquantitative iron in bone marrow and quantitative iron in liver), iron challenge tests (response to IV iron administration), nonrandomized trials (efficacy of single-target IV iron intervention), and RCTs (comparing efficacy of 2 different iron targets). No iron intervention trial has been sufficiently powered to assess safety. Therefore, the Work Group sought to recommend iron targets that balance efficacy with assumptions regarding safety.

***Serum ferritin level greater than 200 ng/mL.*** Earlier versions of KDOQI guidelines recommended a target ferritin level greater than 100 ng/mL. Two RCTs provide comparative information on iron status targets for IV iron therapy (Table 23). In 1 RCT, patients with HD-CKD randomized to maintain TSAT at 20% to 30% achieved a mean serum ferritin level of 297 ng/mL compared with those randomized to a TSAT of 30% to 50%, who achieved 730 ng/mL.[148] Patients in the higher TSAT target group showed a mean 40% reduction in ESA dose compared with those in the lower group. However, the trial was small; iron status targets were defined by TSAT, not ferritin level; and ferritin level in the high-target TSAT group increased throughout the trial and had not reached a steady state by the end of study. In the second trial, patients with HD-CKD assigned to a 200-ng/mL ferritin target compared with those assigned to a 400-ng/mL target achieved mean ferritin levels of 299 compared with 469 ng/mL, respectively. Patients in the higher serum ferritin group had final ESA doses 28% lower than those in the lower ferritin group.[149]

Other available evidence reflects the likelihood of responsiveness to IV iron, but affords little information on the comparative safety and efficacy of iron status targets. Patients with high baseline ferritin levels (mean, 930 ng/mL) were administered IV iron if TSAT was less than 50% and ferritin level was less than 1,000 ng/mL. After receiving an average IV iron dose of 38 mg per week for 12 months, patients showed an increase in ferritin (mean, 1,383 ng/mL) and TSAT (from 27% to 36%) values and a 25% ESA dose decrease.[150] Bone marrow examination in patients with HD-CKD may reveal little or no stainable iron in patients with ferritin levels greater than 100 ng/mL,[98] particularly in patients with evidence of inflammation.[99] It has been reported that IV iron challenge is associated with a positive response (an increase in reticulocyte or Hb values or a decrease in ESA dose) in many patients with serum ferritin levels greater than 100 ng/mL (Table 24).[151-156]

Taken together, the evidence suggests that greater efficacy may be achieved if the lower limit of the ferritin target were greater than the 200 ng/mL threshold. However, given the absence of reliable safety information in clinical trials, uncertainty about the relevance of results from uncontrolled trials, bone marrow iron examination, IV iron challenge studies to iron treatment targets, and the concern for the risk for iron overload, the statement that serum ferritin levels generally should be maintained at greater than 200 ng/mL reflects acceptable—if not maximal—efficacy and a cautious consideration for patient safety.

***TSAT greater than 20%.*** The recommended treatment target of TSAT is 20%, similar to previous KDOQI recommendations. In a single RCT comparing higher to lower TSAT targets,

**Table 24. Value of Baseline Ferritin for Assessing Likelihood of Response to IV Iron Therapy in the HD-CKD Population**

| Author, Year | N | Range (mean) of Baseline Ferritin (ng/mL) | Range (mean) of Baseline TSAT (%) | Challenge: Agent | Challenge: Average Dose / Cumulative Dose | Challenge: Duration | Outcome (Definition of Response) | Responders: Pretreatment Ferritin (ng/mL) [a] | Nonresponders: Pretreatment Ferritin (ng/mL) [a] | Ferritin Threshold (ng/mL) | Sensitivity [b] | Specificity [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Ferritin* | | | | | | | | | | | | |
| Fishbane, 1996 [152] | 47 | <600 (141 [d]) | (22.1 [d]) | IV iron dextran | 100 mg | 10 HD sessions | ↑ Hct ≥5% or ↓ ESA dose ≥10% In 2 mo | 66% | 34% | <500 | 100% | 0% |
| | | | | | | | | | | <300 | 90% | 18% |
| | | | | | | | | | | <200 | 77% | 37% |
| | | | | | 1,000 mg | | | 120 ± 116 | 182 ± 121 | <150 | 71% | 69% |
| | | | | | | | | | | <100 | 48% | 75% |
| | | | | | | | | | | <50 | 37% | 75% |
| Lin, 2001 [161] | 32 | 100-500 (210 ± 110) | 12.3-45.6 (27.9 ± 10.8) | IV ferric oxide | 40 mg | 24 HD sessions | ↑ Hb ≥1 g/dL in 8 wk | 81% | 19% | <400 | 96% | 17% |
| | | | | | | | | | | <300 | 84% | 18% |
| | | | | | 960 mg | | | 214 ± 107 | 192 ± 128 | <200 | 50% | 33% |
| Mittman, 1997 [155] | 77 | <600 (139 [d]) | <50 (23.6 [d]) | IV iron dextran | 500 mg | 1 HD session | ↑ CRI [e] ≥1% in 2 wk | 88% | 12% | <100 | 38% | 53% |
| | | | | | | | | 125 ± 100 | 141 ± 163 | | | |
| Mitsuiki, 2003 [159] | 27 | 10-200 [f] (84 [d]) | 10-45 [f] (27.7 [d]) | IV chondroitin sulfate-iron colloid | 40 mg | Weekly for 8 wk | ↑ Hb ≥1 g/dL in 8 wk | 63% | 37% | <100 | 65% | 60% |
| | | | | | 320 mg | | | 78 ± 63 | 93 ± 74 | | | |
| *Ferritin + Additional Indices* | | | | | | | | | | | | |
| Tessitore, 2001 [154] | 125 | (201 [d]) | (22.3 [d]) | IV sodium ferric gluconate complex | 31 or 62 mg | Each HD session 6-19 wk | ↑ Hb ≥15% in 6-19 wk | 41% | 59% | <50 and Hypo [g] >6% | 82% | 89% |
| | | | | | | | | | | <100 and TSAT <20% | 69% | 61% |
| | | | | | 682-1,770 mg | | | 165 ± 115 | 225 ± 127 | <100 | 35% | 78% |
| | | | | | | | | | | <50 | 20% | 95% |
| Chuang, 2003 [153] | 65 | <500 (230 [d]) | (38.1 [d]) | IV iron saccharate | 100 mg | TIW for 4 wk then every 2 wk for 5 mo | ↑ Hct ≥3% or ↓ ESA ≥30% in 6 mo | 65% | 35% | <300 | 83% | 57% |
| | | | | | | | | | | <300 and CHr <28 pg | 63% | 93% |
| | | | | | 2,200 mg | | | 195 ± 137 | 293 ± 131 | >300 and CHr >28 pg | 52% | 98% |

Footnotes:
a. Mean serum ferritin of subgroup prior to iron challenge.
b. Sensitivity refers to the ratio of (individuals with the outcome who have the test threshold) divided by (all individuals with the outcome). Outcome refers to a response as defined by each study.
c. Specificity refers to the ratio of (individuals without the outcome who do not have the test threshold) divided by (all individuals without the outcome). Outcome refers to a response as defined by each study.
d. Calculated.
e. CRI = reticulocyte count multiplied by the Hct divided by 40.
f. Estimated from graph.
g. Hypochromic erythrocytes

patients randomized to a target TSAT of 30% to 50% demonstrated a 40% reduction in ESA dose compared with those assigned to a target of 20% to 30% (Table 23).[148] As is the situation for serum ferritin level, other sources of evidence are indirect and of uncertain value in setting TSAT targets. In an uncontrolled prospective trial described previously, patients with high baseline ferritin levels (mean, 930 ng/mL) were administered IV iron if TSAT was less than 50% and ferritin level was less than 1,000 ng/mL. After receiving an average IV iron dose of 38 mg/wk for 12 months, patients showed an increase in ferritin (mean, 1,383 ng/mL) and TSAT (from 27% to 36%) values and a 25% ESA dose decrease.[150] Patients with a TSAT of 20% or greater may still show absent bone marrow iron (Table 25) or respond to IV iron challenge (Table 26).[98,99,151-156] The statement that TSAT generally should be maintained at greater than 20% therefore

**Table 25. Value of Ferritin in Assessing Iron Storage Excess or Deficiency**

| Author, Year | N | CKD Stage | Range (mean) of Concurrent TSAT (%) | Range (mean) of Concurrent Ferritin (ng/mL) | Test Organ | Iron Determination | Test Result Scale | Outcome Definition | Most Recent Iron Therapy | Ferritin Threshold (ng/mL) | Sensitivity | Specificity | Patient Population |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Iron Excess* | | | | | | | | | | | | | |
| Canavese, 2004 [163] | 40 | HD-CKD | 7-86 (33 ± 15) | 14-886 (361 ± 224) | Liver | SQUID (quantitative hepatic iron) | µg/g wet weight | Iron excess: >400 µg/g hepatic iron | None for 6 mo (n = 10) None for 2 mo (n = 30) | >340 | 57% | 75% | Relatively unselected, mean Hb 11.4 g/dL, mean albumin 3.6 g/dL |
| | | | | | | | | | | >450 | 46%[c] | 82% | |
| | | | | | | | | | | >500 | 39%[c] | 92% | |
| | | | | | | | | | | >600 | 25%[c] | 100% | |
| *Iron Deficiency* | | | | | | | | | | | | | |
| Fernandez-Rodriguez, 1999 [98] | 63 | HD-CKD PD-CKD | (18.1 ± 16.3) | (273.1 ± 357) | Bone marrow | Stainable iron in aspirate (qualitative) | 0 to +3 | Iron deficiency: 0 stainable iron | No IV iron for 3 mo | <600 | 98% | 14% | Relatively unselected, mean Hb 10.6 g/dL, mean albumin 3.9 g/dL |
| | | | | | | | | | | <300 | 92% | 36% | |
| | | | | | | | | | | <200 | 86% | 55% | |
| | | | | | | | | | | <150 | 81% | 65% | |
| | | | | | | | | | | <100 | 72% | 80% | |
| | | | | | | | | | | <50 | 50% | 95% | |
| Kalantar-Zadeh, 1995 [99] | 25 | HD-CKD PD-CKD ND-CKD Tx-ND-CKD | 4-50 | 19-1,840 | Bone marrow | Stainable iron in aspirate (qualitative) | 0 to +5 | Iron deficiency: 0 to +1 stainable iron | None for 13-30 d | <200 | 50% | 87% | Selected for unexplained Hb <11 g/dL; mean albumin 2.8 g/dL, only 4 patients with albumin >3.4 g/dL |

Footnotes:
a. Sensitivity refers to patients with the Test Threshold Ferritin who havethe Outcome Definition / (patients with Test Threshold Ferritin who have the Outcome Definition plus those with Test Threshold who do not have the Outcome Definition).
b. Specificity refers to patients without the Test Threshold Ferritin who do not have the Outcome Definition / (patients without the Test Threshold Ferritin who do not havethe Outcome Definition plus those with the Test Threshold who do not have the Outcome Definition).
c. Estimated from graph.

**Table 26. Value of Baseline TSAT for Assessing Likelihood of Response to IV Iron Therapy in the HD-CKD Population**

| Author, Year | N | Range (mean) of Baseline TSAT (%) | Range (mean) of Baseline Ferritin (ng/mL) | Challenge: Agent | Challenge: Average Dose / Cumulative Dose | Challenge: Duration | Outcome (Definition of Response) | Responders: Pretreatment TSAT (%) [a] | Nonresponders: Pretreatment TSAT (%) [a] | TSAT Threshold (%) | Sensitivity [b] | Specificity [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Fishbane, 1996 [152] | 47 | (22.1 [d]) | <600 | IV iron dextran | 100 mg | 10 HD sessions | ↑ Hct ≥5% or ↓ ESA dose ≥10% in 2 mo | 66% | 34% | <30 | 96% | 11% |
| | | | | | | | | | | <27 | 92% | 22% |
| | | | | | | | | | | <24 | 88% | 44% |
| | | | | | 1,000 mg | | | 19.4 ± 11.8 | 27.4 ± 19.4 | <21 | 81% | 63% |
| | | | | | | | | | | <18 | 58% | 75% |
| | | | | | | | | | | <15 | 16% | 88% |
| Lin, 2001 [161] | 32 | 12.3-45.6 (27.9 ± 10.8) | 100-500 (209 ± 109) | IV ferric oxide | 40 mg | 24 HD sessions | ↑ Hb ≥1 g/dL in 8 wk | 81% | 19% | <35 | 77% | 0% |
| | | | | | | | | | | <30 | 62% | 17% |
| | | | | | 960 mg | | | 28.5 ± 11.7 | 25.1 ± 5.1 | <25 | 46% | 50% |
| | | | | | | | | | | <20 | 31% | 88% |
| Mittman, 1997 [155] | 79 | <50 (23.6 [d]) | <600 (139 [d]) | IV iron dextran | 500 mg | 1 HD session | ↑ CRI [e] ≥1% in 2 wk | 11% | 86% | <20 | 50% | 60% |
| | | | | | | | | 21 ± 12 | 24 ± 10 | | | |
| Mitsuiki, 2003 [159] | 27 | 10-45 [f] (27.7 [d]) | 10-220 [f] (84 [d]) | IV chondroitin sulfate-iron colloid | 40 mg | Weekly for 8 wk | ↑ Hb ≥1 g/dL in 8 wk | 63% | 37% | <30 | 82% | 70% |
| | | | | | 320 mg | | | 23.7 ± 6.4 | 34.5 ± 7.8 | <20 | 35% | 100% |
| Tessitore, 2001 [154] | 125 | (22.3 [d]) | (201 [d]) | IV sodium ferric gluconate complex | 31 or 62 mg | Each HD session 6-19 wk | ↑ Hb ≥15% in 6-19 wk | 41% | 59% | <19 | 59% | 78% |
| | | | | | 682-1,770 mg | | | 17.7 ± 6.6 | 25.4 ± 8.4 | | | |

Footnotes:
a. Mean TSAT of subgroup prior to iron challenge.
b. Sensitivity refers to the ratio of (individuals with the outcome who have the test threshold) divided by (all individuals with the outcome). Outcome refers to a response as defined by each study.
c. Specificity refers to the ratio of (individuals without the outcome who do not have the test threshold) divided by (all individuals without the outcome). Outcome refers to a response as defined by each study.
d. Calculated weighted average baseline values of responders and nonresponders.
e. CRI = reticulocyte count multiplied by the Hct divided by 40.
f. Estimated from graph.

reflects acceptable, if not maximal, efficacy and a cautious consideration for patient safety.

***CHr greater than 29 pg/cell.*** Evidence to support a treatment target for CHr is drawn from 2 RCTs comparing the use of CHr with TSAT as an iron target. In the first, patients were assigned to receive IV iron for a CHr less than 29 pg/cell. A control group received IV iron for either TSAT less than 20% or ferritin level less than 100 ng/mL. Ferritin and TSAT were followed up in both groups, and IV iron was withheld in any patient with a TSAT greater than 50% or ferritin level greater than 800 ng/mL. Patients assigned to CHr targets showed a lower cost of anemia treatment and a decrease in IV iron use compared with those assigned to TSAT/ferritin targets.[157] In the second RCT, patients assigned to a CHr treatment target of 32.5 pg/cell or greater showed no change in ESA dose, whereas those assigned to a TSAT treatment target of 20% or greater showed a 38% decrease in ESA dose. However, between-group ESA differences did not achieve significance.[158] Functional iron studies have shown that the clinical utility of CHr as a baseline index of response to IV iron challenge varies (Table 27).[151,153-155,159] Results of CHr also may be instrument dependent. The current recommendation of CHr greater than 29 pg/cell is based on the Advia 120 instrument (Bayer Diagnostics Inc).

Other iron status tests have been studied, including percentage of hypochromic red blood cells, zinc protoporphyrin, and soluble transferrin recep-

**Table 27. Value of Baseline CHr for Assessing Likelihood of Response to IV Iron Therapy**

| Author, Year | N | Range (mean) of Baseline CHr (pg) | Range (mean) of Baseline Ferritin (ng/mL) | Challenge: Agent | Challenge: Average Dose / Cumulative Dose | Challenge: Duration | Definition of Response | Responders: Pretreatment CHr (pg) [a] | Nonresponders: Pretreatment CHr (pg) [a] | CHr (pg) Threshold | Sensitivity [b] | Specificity [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mittman, 1997 [155] | 77 | (29.1 [d]) | <600 (139 [d]) | IV iron dextran | 500 mg | 1 HD session | ↑ CRI >1% in 2 wk | 12% | 88% | <28 | 78% | 71% |
| | | | | | | | | | | <27 | 67% | 82% |
| | | | | | | | | 26.4 | 29.5 | <26 | 44% | 88% |
| Mitsuiki, 2003 [159] | 27 | 26-34 [e] (31.2 [d]) | 10-220 [e] | IV chondroitin sulfate-iron colloid | 40 mg | Weekly for 8 wk | ↑ Hct >3% in 8 wk | 63% | 37% | <32 | 100% | 90% |
| | | | | | 320 mg | | | 30.3 ± 1.5 | 32.6 ± 0.7 | | | |
| Tessitore, 2001 [154] | 125 | (30.5 [d]) | (201 [d]) | sodium ferric gluconate complex | 31 or 62 mg | Each HD session 6-19 wk | ↑ Hb ≥15% in 6-19 weeks | 41% | 59% | ≤30 | 69% | 78% |
| | | | | | | | | | | ≤29 | 57% | 93% |
| | | | | | 682-1,770 mg | | | 29.0 ± 2.6 | 31.6 ± 2.0 | ≤28 | 37% | 97% |
| | | | | | | | | | | ≤26 | 10% | 100% |
| Chuang, 2003 [153] | 65 | (28.0 [d]) | <500 | IV iron saccharate | 100 mg | TIW for 4 wk then every 2 wk for 5 mo | ↑Hct by 3% or ↓ ESA by 30% in 6 mo | 65% | 35% | <28 | 78% | 87% |
| | | | | | 2,200 mg | | | 27.2 ± 1.6 | 29.6 ± 1.7 | | | |
| Fishbane, 1997 [151] | 32 | (27.0 [d]) | <600 | IV iron dextran | 1,000 mg | 1 HD session | ↑ CRI ≥1% in 2 wk | 22% | 78% | <26 | 100% | 80% |
| | | | | | | | | 23.7 | 27.9 | | | |

Footnotes:
a. Mean CHr of subgroup prior to iron challenge.
b. Sensitivity refers to Iron Responders with the Test TSAT Threshold / (Iron Responders with the Test TSAT Threshold plus Iron Responders who do not meet Test TSAT threshold).
c. Specificity refers to Nonresponders without the Test TSAT Threshold / (Nonresponders without the Test TSAT Threshold plus Nonresponders with the Test TSAT threshold).
d. Calculated.
e. Estimated from graph.

**Table 28. Mean Monthly Dose of Iron in Adult Prevalent HD-CKD Patients on ESA Therapy**

| Author, Year Study Design | N[a] | Follow-up (mo) | Intervention Arm 1 | Intervention Arm 2 | Outcome | Type of Iron Given / Mean Dose[b] (mg/mo) | Mean Ferritin during Steady State (ng/mL) |
|---|---|---|---|---|---|---|---|
| Brimble, 2003 [183] RCT | 167[c] | 8 | Protocolized anemia management care by study team Target Hb: 11-12.5 g/dL | Usual care by primary nephrologist and nurse clinician Target Hb: 11-12.5 g/dL | Primary: Proportion of patients with Hb values in target range | Iron sucrose / 148 vs. 152 | 200 vs. 220 |
| Tolman, 2005 [139] RCT | 162 | 9 | SC darbepoetin-α 1x/wk Target Hb: 11-12 g/dL | SC epoetin-β 1x/wk Target Hb: 11-12 g/dL | Primary: ESA dose at 9 mo | Iron sucrose / 140-240[d] (range) | 493 (median for Arm 2 weeks 3-9) |
| Fishbane, 2001 [157] RCT | 138 | 6 | If ferritin <100 ng/mL or TSAT <20%, IV iron dextran, 100 mg on 10 consecutive HD sessions | If CHr <29 pg, IV iron dextran, 100 mg on 10 consecutive HD sessions | Primary: Iron management (Hct, ESA dose, iron dose requirement, serum ferritin, TSAT, CHr) | Iron dextran / 260 vs.120 | 310 vs. 280 |
| Cervelli, 2005 [184] Crossover RCT | 24 | 6[e] | SC darbepoetin-α 1x/wk Target Hb: 11-13 g/dL | IV darbepoetin-α 1x/wk Target Hb: 11-13 g/dL | Darbepoetin dose and dose variability | Iron polymaltose / 148 vs. 88 | 705 vs. 593 |
| Besarab, 1999 [160] Non-RCT | 24 | 18 | Maintenance (continuous) iron Target TSAT: 30%-50% Target Hb: 10-11 g/dL[f] | As-needed (Intermittent) iron Iron therapy if TSAT <20% or ferritin <200 ng/mL Target Hb: 10-11 g/dL [g] | Primary: ESA dose | Iron dextran / 208 vs.160 | 645 vs. 312 (Arm1: week 15 and later; Arm 2: all weeks) |

Footnotes:
a. N at completion.
b. Reflects the average monthly dose of IV iron administered. (One month = 4 weeks).
c. Patients enrolled >5 months
d. Estimated from graph
e. The first 4 months of each 6-month study period were designated as dose titration phases, the final 2 months were designated as evaluation periods for dosing efficiency.
f. IV iron dextran 300-5,000 mg to TSAT >30%, followed by 25-100 mg every 1-2 weeks to maintain TSAT between 30%-50%. Maximum monthly dose 400 mg. No iron given if ferritin ≥800 ng/mL.
g. IV iron dextran 100 mg on 10 consecutive HD sessions when TSAT <20% or ferritin level <200 ng/mL.

tors. Evidence to support these tests as targets for iron treatment is poor or unavailable.

***Treat-to-target approaches.*** There are 2 widely used and effective approaches to IV iron treatment: (1) periodic iron repletion, consisting of a series of IV iron doses administered episodically to replenish iron stores whenever iron status tests decrease to less than target range; or (2) continuous maintenance treatment, consisting of smaller doses administered at regular intervals to maintain iron status tests stable within target. No RCTs are available to compare the efficacy and safety of these 2 approaches; however, the total cumulative dose may not differ between them.[160] In studies that achieved steady-state ferritin levels and reported iron doses administered, the average IV iron dose needed to maintain a stable ferritin level (signifying achievement of the goal of neutral iron balance) appears to be in the range of 22 to 65 mg/wk (Table 28). Higher doses may lead to progressive increases in serum ferritin levels in some patients.[148,156]

### *Iron Targets in Patients With ND-CKD and PD-CKD*

Evidence to support an iron treatment target in patients with ND-CKD and PD-CKD is lacking. There are no RCTs comparing iron targets in these patient populations. Dialysis-related blood loss renders evidence from patients with HD-CKD unsuitable for application to patients with ND-CKD or PD-CKD. Thus, in these patients, the Work Group recommends iron treatment targets that reflect a conservative estimate of efficacy and a cautious approach to patient safety.

### ***Upper Level of Ferritin***

The statement *There is insufficient evidence to recommend routine administration of IV iron if ferritin level if greater than 500 ng/mL* reflects the findings of the Work Group that: (1) no RCTs have compared the safety and efficacy of ferritin targets greater than 500 ng/mL with the safety and efficacy of lower ferritin targets, (2) few studies have examined the efficacy of IV iron at ferritin levels greater than 500 ng/mL, (3) no study has examined either efficacy or safety beyond surrogate outcomes, (4) no information from interventional trials is available about the safety of ferritin targets greater than 500 ng/mL, and (5) sufficient evidence exists to suggest that tissue iron stores in patients with ferritin levels greater than 500 ng/mL are normal to greater than normal.

No evidence is available to compare ferritin targets greater than 500 ng/mL with lower ferritin targets. That is, no RCTs have assigned patients to a ferritin target greater than 500 ng/mL and compared results with those in patients assigned to a ferritin target less than 500 ng/mL. In the absence of comparisons between groups in intention to treat, no conclusions can be drawn to assess RRs and benefits of IV iron therapy at the higher ferritin level.

The efficacy of IV iron in patients with baseline ferritin levels greater than 500 ng/mL has been examined in a single uncontrolled study.[150] Described previously, this trial administered IV iron to patients for 12 months, withheld iron for patients with a ferritin level greater than 1,000

ng/mL or TSAT greater than 50%, and found that mean ferritin level increased from 930 ng/mL at baseline to 1,383 ng/mL at 12 months and ESA dose decreased by 25%. However, the lack of a control group renders conclusions about the ESA dose change uncertain. Analysis of uncontrolled anemia interventional trials is subject to target bias. That is, patients who are most likely to survive and complete the trial likely bear a low disease burden and are, in turn, most likely to show higher Hb and lower ESA doses. Conversely, patients who are least likely to complete the trial bear a high disease burden and therefore are most likely to show worsening anemia and higher ESA doses. Successful trial completion therefore is associated with higher Hb levels and lower ESA doses, regardless of intervention.

Other efficacy trials have examined the functional relationship between baseline ferritin level and likelihood of a surrogate hematologic response to IV iron challenge (Table 24). However, none of these studies examined patients with baseline ferritin values greater than 500 ng/mL. Moreover, because efficacy of IV iron in the available interventional and functional iron studies is limited to surrogate outcomes (reticulocyte increase, Hb level increase, or ESA dose decrease),[152-155,161,162] evidence of direct patient benefit (including improved QOL, health, or survival) of IV iron administration in patients at ferritin values greater than 500 ng/mL is lacking.

Information on potential harm to patients similarly is lacking. Again, evidence to permit reliable assessment of risks and benefits can only come from RCTs assigning patients to intent-to-treat ferritin targets greater than 500 ng/mL compared with less than 500 ng/mL, with adequate power to assess both efficacy and safety.

Evidence that tissue iron stores in patients with ferritin levels greater than 500 ng/mL are adequate to greater than normal includes results from surveys in the general US population and studies of bone marrow iron or liver iron in patients with CKD. Among randomly selected individuals in the general US population, ferritin values greater than 500 ng/mL lie at or greater than the 95$^{th}$ percentile among males aged 15 to 59 years and far exceed the 95$^{th}$ percentile among females of all ages.[163] However, findings in the general population do not necessarily apply to patients with CKD. Among patients with CKD undergoing bone marrow examination, no patient with a ferritin level greater than 500 ng/mL showed absent marrow iron stores.[98,99] Finally, among patients with HD-CKD undergoing tissue iron determination by means of magnetic susceptometry, ferritin levels greater than 500 ng/mL were associated with hepatic non–heme-iron concentrations greater than the upper limit of normal.[163] In short, ferritin values exceeding 500 ng/mL likely represent supraphysiological results in the general population and tissue iron sufficiency or excess in patients with HD-CKD.

Thus, no current evidence is available to support routine treatment of patients with serum ferritin levels greater than 500 ng/mL. Rather, clinicians should judge the individual patient's clinical status and ESA responsiveness and base iron treatment decisions on this assessment. In particular, when serum ferritin level is greater than 500 ng/mL while the concurrently measured TSAT is less than 20%, iron deficiency may be present and a course of iron treatment may be considered.

In short, no current evidence is available to support treating most patients with serum ferritin levels greater than 500 ng/mL. A therapeutic response to a 1,000-mg IV iron challenge in a patient with a ferritin level greater than 500 ng/mL is unlikely. Because iron stores are adequate or elevated in patients with ferritin values greater than 500 ng/mL, the long-term safety of iron therapy at target ferritin values exceeding 500 ng/mL is untested, and efficacy results of IV iron therapy are limited to surrogate outcomes rather than direct patient benefits, the Work Group favors limiting routine iron treatment to patients with serum ferritin values less than 500 ng/mL. Accordingly, the conclusion of the Work Group is that *there is insufficient evidence to recommend routine administration of IV iron if ferritin level is greater than 500 ng/mL.*

The finding of a TSAT less than 20% coupled with a ferritin level greater than 500 ng/mL poses a particularly difficult problem for clinicians.[157] This situation may be caused by iron test variability,[157] falsely low TSAT results, inflammation, or reticuloendothelial iron blockade. Evidence on the risks and benefits of IV iron therapy in these patients is almost entirely lacking. However, the statement that *There is*

**Table 29A. Comparative RCTs of IV versus PO Iron Administration and Efficacy of Anemia Management in the HD-CKD and PD-CKD Populations**

| Author, Year | N | CKD Stage | Mean Follow-up (mo) | Applicability | Baseline | | | | Intervention | | | ESA Co-Intervention | Clinical Outcome [a] | Result | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Hb (g/dL) | ESA Dose | TSAT (%) | Ferritin (ng/mL) | IV Agent / PO Agent | Dose | Frequency | Description | Definition | Actual Value IV vs. PO | Statistical Significance | |
| Fishbane, 1995 [156] | 52 | HD-CKD | 4 | ↑↑ | 10.8 | 7,100 IU* | 23 | 191 | Iron dextran | 100 mg over 2 min | 2x/wk | IV ESA adjusted [b] | Mean Hb (g/dL) | 11.5 vs. 10.6 | + | ⊙ |
| | | | | | 10.6 | 6,750 IU* | 21 | 179 | Ferrous sulfate (N = 21) | 325 mg | TID | | Mean ESA dose (IU/treatment) | 4,050 vs. 7,563 | + | |
| | | | | | | | | | Iron polysaccharide (N = 11) | 150 mg | BID | | | | | |
| Fudin, 1998 [167] | 30 | HD-CKD | 26 | ↑↑ | 7.8 | 0 | 21 [c] | 204 | Iron sodium gluconate complex | 62.5 mg | Each HD session | None | Mean Hb (g/dL) | 11.0 vs. 6.5 [c] | nd | ⊙ |
| | | | | | 6.8 | 0 | 20 [c] | 268 | Ferrous sulfate | 160 mg | Daily | | | | | |
| Macdougall, 1996 [166] | 25 | HD-CKD PD-CKD | 4 | ↑↑ | 7.3 | 0 | 26 | 345 | Iron dextran | 5 mL (~250 mg) over 25–30 min | Every 2 wk | SC ESA adjusted [d] | Mean Hb (g/dL) | 11.9 vs. 10.2 | + | ⊙ |
| | | | | | 7.2 | 0 | 27 | 309 | Ferrous sulfate | 200 mg | TID | | Mean ESA dose (IU/kg/16 wk) | 1,202 vs. 1,294 | NS | |

* Per treatment.

Footnotes:
a. Primary outcomes of study given unless otherwise noted.
b. Adjusted to target Hct 30%-34%.
c. Estimated from graph.
d. ESA dose kept stable for at least 8 weeks. Dose decreased if Hb >12 g/dL or dose doubled if Hb had not increased by 1 g/dL 8 weeks.

Coding of Outcomes:
+ Statistically significant benefit seen for comparison of arm 1 vs. arm 2, unless otherwise noted

*insufficient evidence to recommend routine administration of IV iron if ferritin level is greater than 500 ng/mL* does not preclude IV iron administration in selected patients when, in the clinician's judgment, a trial of iron therapy is warranted.

It is important to reiterate that the statement *There is insufficient evidence to recommend routine administration of IV iron if ferritin level is greater than 500 ng/mL* refers to ferritin targets, not to achieved or acquired ferritin levels. Ferritin levels exceeding 500 ng/mL are often achieved as a result of iron therapy given to patients with lower baseline ferritin levels or may be acquired in the course of infection, inflammation, or other illness. Achieved or acquired ferritin levels are described elsewhere,[164] but are not the subject of this guideline statement.[165]

### *Route of Administration*

Evidence to support the statement *The preferred route of iron administration is IV in patients with HD-CKD* consists of results from 3 RCTs comparing IV iron with oral iron administration (Table 29A–Table 31A), including 2 that incorporated a placebo or nontreatment control arm (Table 30). A fourth RCT compared oral iron administration to no-iron control (Table 30). In 2 of these 4 RCTs, patients were assigned to IV or oral iron treatment while undergoing ESA therapy.[159,166] By study completion, those assigned to IV iron showed a greater Hb level, lower ESA dose, or both compared with those assigned to oral iron (Table 29A, Table 31A). In the third RCT, patients not receiving ESA showed an increase in Hb levels from 7.8 to 11.0 g/dL after IV iron, but no change in Hb levels was

**Table 29B. Comparative RCTs of IV vs. PO Iron Administration and Efficacy of Anemia Management in the ND-CKD Population**

| Author, Year | N | CKD Stage | Mean Follow-up (mo) | Applicability | Baseline | | | | Intervention | | | ESA Co-intervention | Clinical Outcome [a] | Results | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Hb (g/dL) | ESA Dose [e] | TSAT (%) | Ferritin (ng/mL) | IV Agent / PO Agent | Dose | Frequency | Description | Definition | Actual Value IV vs. PO | Statistical Significance | |
| Van Wyck, 2005 [169] | 161 | 3-5 | 2 | ↑↑↑ | 10.2 | nd | 16 | 93 | Iron sucrose | 500 mg or 200 mg | 2x or 5x over 14 d | N = 32 patients on ESA unadjusted | % patients with ↑ Hb ≥1 g/dL | 44.0% vs. 28.0% | + | ● |
| | | | | | 10.1 | nd | 17 | 104 | Ferrous sulfate | 325 mg | TID | | Mean ↑ Hb by day 42 (g/dL) | 0.7 vs. 0.4 | + | |
| Charytan, 2005 [172] | 96 | 3-4 [b] | 1.5 | ↑↑ | 9.8 | 0 | 17 | 125 | Iron sucrose | 200 mg | weekly | SC ESA unadjusted | Mean ↑ Hb (g/dL) | 1.0 vs. 0.7 | NS | ⊙ |
| | | | | | 9.7 | 0 | 16 | 103 | Ferrous sulfate | 325 mg | TID | | % patients with ↑ Hb ≥0.8 g/dL and ↑ Fer ≥160 ng/mL (and ↑ TSAT >5%) | 65.0% vs. 0% (44.0% vs. 0%) | + [c] | |
| Stoves, 2001 [171] | 45 | 3-4 [d] | 5.2 | ↑↑ | 9.9 | 0 | nd | 100 | Iron sucrose | 300 mg over 2 hr | monthly | SC ESA adjusted to achieve Hb 12 g/dL | Median ESA Dose (IU/kg/wk) | 41.6 vs. 33.5 | NS | ⊙ |
| | | | | | 9.7 | 0 | nd | 74 | Ferrous sulfate [e] | 200 mg | TDS | | | | | |
| Aggarwal, 2003 [170] | 40 | 4-5 [f] | 3 | ↑ | 5.8 | 0 | 64 | 181 | Iron dextran | 2 mL (100 mg) | 2x/mo | ESA unadjusted | Mean Hb (g/dL) | 10.0 vs. 8.9 | + | ⊙ |
| | | | | | 6.3 | 0 | 60 | 190 | Ferrous sulfate | 200 mg | TID | | | | | |

Footnotes:
a. Primary outcomes of study given unless otherwise noted.
b. Creatinine clearance <40 mL/min, not requiring dialysis.
c. P = 0.00 for both analyses.
d. Individuals with $S_{Cr}$ >2.84 mg/dL, not requiring dialysis.
e. Alternatively, the patients received an equivalent dose of an alternative iron preparation that had been previously tolerated.
f. Statistically significant differences between mean creatinine clearance of IV iron group (6.47 mL/min) and PO iron group (12.02 mL/min) at baseline (p<0.05).

Coding of Outcomes:
+ Statistically significant benefit seen for comparison of arm 1 vs. arm 2, unless otherwise noted

**Table 30. Comparative RCTs of PO Iron Administration versus Placebo/Control and Efficacy of Anemia Management in the HD-CKD and PD-CKD Populations**

| Author, Year | CKD Stage | Follow-up (mo) | N | Baseline | | | | Intervention | | | | Results | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Hb (g/dL) | ESA Dose (IU) | TSAT (%) | Ferritin (ng/mL) | PO Agent / Placebo/Control | Dose | Frequency | ESA Cointervention | Clinical Outcome Definition[a,b] | Actual Value Arm 1 vs. Arm 2 | Statistical Signifi-cance |
| Fudin, 1998 [167] | HD-CKD | 12-26[c] | 24 | 6.8 | 0 | 20[d] | 204 | Ferrous sulfate | 160 mg | Daily | None | Mean Hb at 12 mo (g/dL) | 6.5 vs. 6.0[d] | nd |
| | | | | 6.3 | 0 | 16[d] | 190 | Control | — | — | | | | |
| Macdougall, 1996 [166] | HD-CKD PD-CKD ND-CKD | 4 | 25 | 7.2 | 0 | 27 | 309 | Ferrous sulfate | 200 mg | TID | SC ESA adjusted[e] | Mean Hb (g/dL) | 10.2 vs. 9.9[d] | NS |
| | | | | 7.3 | 0 | 23 | 458 | Control | — | — | | Mean ESA dose (IU/kg/16 wk) | 1,294 vs. 1,475 | NS |
| Markowitz, 1997 [185] | HD-CKD | 3 | 24 iron-deficient patients[f] | 10.1 | 5,714 | 26.5 | 40 | Iron polysaccharide complex | 150 mg | BID | ESA adjusted | Mean Hb (g/dL)[g] | 10.7 vs. 10.5 | NS |
| | | | | 10.4 | 4,850 | 42.6 | 39 | Placebo | 150 mg | BID | | Mean ESA dose (IU)[g] | 6,142 vs. 4,650 | nd |
| | | | 25 iron-replete patients[f] | 11.2 | 4750 | 36.4 | 221 | Iron polysaccharide complex | 150 mg | BID | ESA adjusted | Mean Hb (g/dL)[g] | 7.3 vs. 8.5 | NS |
| | | | | 10.7 | 4,692 | 35.4 | 228 | Placebo | 150 mg | BID | | Mean ESA dose (IU)[g] | 4,417 vs. 4,615 | nd |

Footnotes:
a. Primary outcomes of study given unless otherwise noted.
b. Outcomes reported at final follow-up, unless otherwise noted.
c. 12-month follow-up for control group; 26-month follow-up for oral iron group.
d. Estimated from graph.
e. ESA dose kept stable for at least 8 weeks. Dose decreased if Hb >12g/dL or dose doubled if Hb had not increased by 1 g/dL at 8 weeks.
f. Iron Deficient: Ferritin <100 µg/L; ZPP <90 mmol/mL heme; Hb >10g/dL. Iron Replete: Ferritin <100 µg/L; ZPP >90 mmol/mL heme; Hb >8.3.
g. Primary outcome was change in serum ferritin and ZPP. Results reported at 3-month follow-up before final 2-month period without treatment.

seen in patients assigned to oral iron. Between-group comparisons were not reported.[167] Of the 4 available RCTs, 3 included a placebo-treatment or no-iron-treatment arm. Results showed no difference in final Hb level or ESA dose between oral iron treatment and placebo/control. In summary, evidence in patients with HD-CKD supports 2 conclusions: (1) oral iron administration is not demonstrably more effective than either placebo or no treatment; and (2) IV iron administration is superior to oral iron administration.

A newer form of oral iron that has not been studied widely is heme iron polypeptide. A single RCT of patients with HD-CKD compared treatment with IV iron with treatment with heme iron polypeptide.[168] Uncertainty in the randomization procedure, disproportionately high baseline ESA doses in the oral iron treatment group, a substantial dropout fraction confined to the oral iron treatment group, a significant decrease in serum ferritin levels during 6 months of oral iron treatment, and an undefined IV iron treatment protocol render the results of this trial difficult to interpret. Further studies will be required to provide a basis for recommendations on the use of this agent.

Evidence to support the statement *The route of iron administration can be either IV or oral in patients with ND-CKD or PD-CKD* consists of results from 4 RCTs comparing IV iron with oral iron administration in patients with ND-CKD (Table 29B, Table 31A). The Work Group

**Table 31. Serious AEs of Iron Agents in Patients Naïve to Tested Iron Agent (N > 100)[a]**

| Author, Year | Study Design | N | Population | Dose Size (mg) | IV Rate (mg/min) | Doses (n) [Doses/pt] | Serious ADE Rate (%) Per Patient [Dose] [b] | Definition of Serious AE |
|---|---|---|---|---|---|---|---|---|
| *Iron Dextran* | | | | | | | | |
| McCarthy, 2000 [188] | Retrospective, database review | 254 | HD | 300 | 5-10 | 3,578 [nd] | 0.8 [1st course] | Suspected anaphylactic reaction comprised of wheezing/dyspnea |
| Walters, 2005 [176] | Retrospective, database review | 20,213 [c] | HD and PD | — | — | 20,213 [1] | 0.035 [Test or 1st] | Requiring parenteral administration of epinephrine, corticosteroids, or antihistamines on the same dialysis day |
| *Ferric Gluconate* | | | | | | | | |
| Michael, 2002 [175] | RCT, crossover | 2,534 | HD [d] | 125 | 12.5 | 2,514 [1] | 0.6 [1st] | Drug intolerance, which included anaphlyactoid reaction, hypotension, chills, back pain, nausea, dyspnea/chest pain, facial flushing, rash and cutaneous symptoms of porphyria, and 1 life-threatening event requiring parenteral antihistamine, hydrocortisone, and epinephrine. |
| *Iron Sucrose* [e] | | | | | | | | |
| Aronoff, 2004 [187] | Prospective, cohort | 665 [f] | HD | 100 | 50 | 8,583 [nd] | 0 [NA] | Any event that is fatal or life-threatening, results in or prolongs hospitalization, results in significant disability or incapacity, is unusual, or in opinion of the investigator, presents a significant hazard to the patient. |
| Blaustein, 2003 [188] | Prospective, cohort | 107 | Stage 3-5 (1 PD, 2 HD patients) | 500 | 3.2 | 266 [2] | 0 | Not specified. No adverse reactions requiring parenteral medications or hospitalizations |
| Charytan, 2004 [189] | Prospective, cohort | 130 [f] | HD [d] | 100-200 | 50-100 | ND [nd] [g] | 0 [NA] | Hypotension, wheezing, respiratory stridor, shortness of breath, hypertension, anaphlyaxis, chest tightness |

Footnotes:
a. Modified for K/DOQI use from reference[190]. See Methods for selection criteria.
b. Majority of ADEs occurred during this/these dose(s).
c. Incident subpopulation of 48,509 patient study.
d. <10% of patient with iron dextran allergic history.
e. Included patients with previous intolerance to either iron dextran or ferric gluconate.
f. All patients with previous intolerance to iron dextran and/or ferric gluconate.
g. Median cumulative dose: 1,000 mg; range: 100-5,000 mg.

**Table 31A. IV versus PO Iron Agents in the HD-CKD and PD-CKD Populations**

| Outcome | No. of Studies & Study Design | Total N of Patients | Methodological Quality of Studies | Consistency across Studies | Directness of the Evidence / Applicability | Other Considerations | Summary of Findings: Quality of Evidence for Outcome | Summary of Findings: Qualitative Description of Effect Size | Summary of Findings: Importance of Outcome |
|---|---|---|---|---|---|---|---|---|---|
| Hb/Hct Level / ESA Dose | 3 RCTs | 107 | Some limitations [a] | No important inconsistencies | Direct | Supported by lack of efficacy of oral iron compared to placebo [b] | Moderately High to High | Benefit. The final mean Hb ranged from 0.9 to 4.5 g/dL higher in the IV arms than the PO arms [3 studies]. Mean final ESA dose was lower in IV arms, ranging from -92 IU/kg/16 wk in 1 study and -3,513 IU/treatment in the other study. [2 studies] | Moderate |
| Adverse Events with IV Iron | 31 Prospective and Retrospective Studies | Tested Iron Naïve: 23,903 All patients: 58,578 | The frequently nonspecific nature of IV iron-related AE, the substantial overlap between drug-related AE and dialysis-related AEs (e.g. dizziness, dyspnea, cramps, pruritus, nausea, constipation, diarrhea, and hypotension), and the low anticipated event rate for the most serious ADE's (hypersensitivity) limit assessment of IV iron related AE in most trials. However, when limited to studies where N >100, rates of SAE/hypersensitivity reactions in patients naïve to tested iron agent range from 0-0.8% per patient. [c] | | | | | | High |
| | | | **Balance of Benefit and Harms: Net Benefit of IV Iron** | | | | **Quality of Overall Evidence: Moderately High to High** | | |

Footnotes:
a. All studies are Grade B.
b. 2/3 studies has a placebo/no oral iron arm. Both studies showed no difference in final Hb or ESA dose between oral iron treatment and placebo/control and an increase in mean Hb in the IV arms. A third RCT, with oral iron vs. placebo showed a similar lack of efficacy of oral iron.
c. In the 4 studies where N >100 and patients naïve to tested iron agent, SAE occurred <1% of patients.

rated the evidence from these trials as strong or moderately strong. There are no RCTs in patients with ND-CKD comparing oral iron therapy with placebo or no iron treatment. There are no RCTs in patients with PD-CKD.

The 4 available in ND-CKD RCTs differ substantially in the use, timing, and adjustment of ESA therapy (Table 31B). Three initiated ESA therapy in all study patients at randomization, whereas 1 continued ESA therapy in patients previously treated, but did not initiate ESA therapy in previously untreated patients. One adjusted ESA during the trial to achieve a target Hb level, whereas 3 permitted no ESA dose adjustment or required removal from the trial if ESA therapy initiation or ESA dose increase was needed.

The 4 available RCTs also differ in the dosing, frequency, and duration of IV iron administered. The 4 dosing regimens included 1,000 mg administered in 2 or 5 divided doses over 2 weeks,[169] 200 mg monthly,[170] 300 mg monthly,[171] or 1,000 mg in 5 doses over 5 weeks.[172]

Finally, the 4 available RCTs differ substantially in severity of anemia at baseline, ranging from a mean Hb level of 5.8 to 6.3 g/dL in 1 trial[170] to 9.7 to 10.2 g/dL in the remaining 3 trials.

Between-group differences showing superiority of IV iron over oral iron were seen in 2 of the 4 available RCTs (Table 31B). The 2 studies that initiated ESA therapy in patients with moderate anemia found no difference between patients assigned to IV iron compared with oral iron.[171,172] The 2 trials that showed differences either initiated ESA therapy simultaneously with iron therapy in patients with severe anemia[170] or maintained prior ESA status without adjustment

**Table 31B. IV versus PO Iron Agents in the ND-CKD Population**

| Outcome | No of Studies & Study Design | Total N of Patients | Methodological Quality of Studies | Consistency across Studies | Directness of the Evidence, including Applicability | Other Considerations | Summary of Findings: Quality of Evidence for Outcome | Summary of Findings: Qualitative Description of Effect Size | Summary of Findings: Importance of Outcome |
|---|---|---|---|---|---|---|---|---|---|
| Hb/Hct Level / ESA Dose | 4 RCTs | 342 | No serious limitations [a] | Some inconsistencies [b] | Some uncertainty [c] | Sparse data [d] | Moderately High | Likely Benefit. The final mean Hb ranged from 0.3 to 1.1 g/dL higher in the IV arms compared with the PO arms. 2/3 studies were statistically significant. 1 study evaluated mean ESA dose and found no difference with IV Iron. | Moderate |
| Adverse Events | 4 RCTs | 342 | Fewer gastrointestinal complaints in IV vs. oral iron arm. Five patients in two trials, all women with low body mass, experienced adverse reactions to administration of IV iron, including hypotension, cramping, arthralgia and myalgia; rates of SAE/hypersensitivity reactions similar to the dialysis population are likely to apply to non-dialysis population. | | | | | | High |
| | | | **Balance of Benefit and Harms: Trade Off between Efficacy and Potential for More Clinically Serious Harms** | | | | **Quality of Overall Evidence: Moderately High** | | |

Footnotes:
a. 1 Grade A and 3 Grade B studies.
b. 2 of 3 studies showed statistically significant improvement in Hb level with IV iron, while 1 showed non-significant increase; evaluation for consistency on Δ ESA dose is not applicable given only 1 study.
c. 4 available RCTs differ substantially in the use, timing and adjustment of ESA therapy, timing and dose of iron therapy, and severity of anemia at baseline.
d. Lack of RCTs on efficacy of oral vs. placebo or no treatment in the ND-CKD population.

in patients with moderate baseline anemia.[169] In the latter study, superiority of IV iron over oral iron was greatest among patients with ESA therapy and baseline Hb level less than 9.0 g/dL.[169]

Other outcomes compared in the 4 available RCTs included rate of decline in kidney function, QOL, adverse GI effects, dietary protein and energy intake, and adherence to prescribed therapy. Compared with patients assigned to oral iron therapy, those assigned to IV iron treatment showed no difference in rate of decrease in kidney function,[169-171] no difference in QOL,[169] fewer GI symptoms,[169-172] no difference in protein and energy intake,[171] and better adherence to prescribed therapy.[169] Five patients in 2 trials, all women with low body mass, experienced adverse reactions to administration of IV iron, including hypotension, cramping, arthralgia, and myalgia.[169,171]

Given the variability in trial design, inconsistency of results, potential for adverse effects of IV iron, lack of information on potential adverse effects of oral iron, surrogate nature of tested outcomes in iron intervention trials, paucity of information on patient preference and adherence to treatment recommendations, and lack of information on the efficacy of oral iron compared with placebo or no-iron treatment, the Work Group concluded that the strength of available evidence is insufficient to support a guideline statement on the use of IV versus oral iron in patients with ND-CKD. However, in the opinion of the Work Group, *the route of iron administration can be either IV or oral in patients with ND-CKD or PD-CKD*.

Because no RCTs are available to compare IV iron with oral iron in patients with PD-CKD, the Work Group considered whether to regard the PD-CKD patient population as similar to ND-CKD, similar to HD-CKD, or too dissimilar from either to justify a recommendation. On the basis of the assumption that patients with PD-CKD do not experience ongoing dialysis-associated blood loss, the Work Group reasoned that patients with PD-CKD resemble the ND-CKD population and differ from patients with HD-CKD. Thus, patients with PD-CKD are included in the current opinion-based CPR.

### *Hypersensitivity Reactions*

There currently are 3 forms of IV iron that are widely available: iron dextran, sodium ferric gluconate, and iron sucrose. All forms of IV iron may be associated with acute AEs, occasionally severe, comprised of hypotension with or without other symptoms and signs. The cause of the reactions is incompletely understood. Immune mechanisms (including mast cell–mediated processes leading to a clinical syndrome resembling anaphylaxis) may have a role in some cases. In others, the iron agent may release bioactive, partially unbound iron into the circulation, resulting in oxidative stress and hypotension (labile or free iron reactions). The pathogenesis may differ depending on the type of IV iron. Anaphylactoid reactions appear to occur more frequently with iron dextran,[173] and labile or free iron reactions occur more frequently with nondextran forms of iron.[174]

The reported frequency of acute drug AEs depends in large part on the structure and rigor of the experimental design used. Direct patient observation after administration of an IV iron agent permits the most reliable assessment. For example, in a double-blind placebo-controlled trial of sodium ferric gluconate in 2,534 HD patients,[175] investigators directly observed patients for evidence of reactions after blinded IV administration of drug or placebo. If, in the opinion of the investigator, a reaction was demonstrated, serum tryptase levels were measured to evaluate for mast cell–mediated hypersensitivity.

Prospective single-arm clinical trials also contribute information on drug-related AEs in the target population (Table 31). In reports of these trials, observation for drug-related AEs was performed by the study nurse or a staff nurse or, alternatively, the method of observation was not specified.

Retrospective study designs use review of medical records or large-scale electronic databases to identify potential drug-related AEs after the fact.[176,177]

Finally, pharmacovigilance surveillance studies use national voluntary reporting data sources, including the Freedom of Information Act database administered by the FDA, to evaluate AE profiles of IV iron agents. Pharmacovigilance studies yield unreliable information about abso-

lute AE rates and are susceptible to uncontrolled observer bias, but afford the advantage of detecting rare events, shedding light on common characteristics of low-frequency events, and suggesting relative rates of AEs. However, they do not permit statistical comparison of AE rates for different IV iron agents.

The frequently nonspecific nature of IV iron–related AEs, the substantial overlap between drug-related AEs and dialysis-related AEs (eg, dizziness, dyspnea, cramps, pruritus, nausea, constipation, diarrhea, and hypotension), and the low anticipated event rate for the most serious AEs pose significant challenges for each study design described. The single greatest problem is the absence of generally accepted criteria to identify IV iron–related AEs and distinguish hypersensitivity from nonhypersensitivity reactions. The absence of criteria for IV iron–related AEs introduces potential observer bias into both prospective and retrospective trials. Pharmacovigilance studies also are subject to observer bias because only AEs thought to be drug related are reported. As long as neither descriptive criteria nor objective markers are available, designation of an AE as drug related likely will remain somewhat subjective. Although blinding the intervention so that neither the investigator nor the patient is aware of the identity of the agent administered improves the objectivity of AE reporting, event rates are sufficiently low to preclude comparative trials that are logistically feasible. For example, to conduct an RCT that would be adequately powered to compare serious AE rates between 2 iron agents would require enrolling more than 10,000 patients, an unlikely prospect. Accordingly, comparative assessment of safety is likely to continue to rely on retrospective chart review, analysis of large-scale medical databases, and pharmacovigilance reports.

Evidence is available from 2 retrospective reports, including 1 in patients with CKD. Both analyses concluded that the rate of life-threatening reactions to iron dextran administration is 0.6% to 0.7%.[178,179] Two additional studies used large medical databases to further identify the nature and consequences of life-threatening reactions after IV iron dextran.

***Fletes et al 2001.***[177] This study identified 165 suspected drug-related AEs after 841,252 exposures to iron dextran in patients with HD-CKD (rate per exposure, 0.02%). There was 1 fatal event. Although many AEs followed administration of a test dose or first dose, this study identified serious AEs in patients who had successfully received previous test or treatment doses. The majority of the non-naïve patients who experienced AEs after iron dextran administration did so at the time of the first dose of a planned series, suggesting that the risk for first-dose AE may recur in prevalent patients after an interval free from iron dextran exposure.[177]

***Walters and Van Wyck 2005.***[176] The database of a large dialysis provider was examined to identify episodes of iron dextran–induced anaphylaxis sufficiently severe to require use of resuscitative medications. They found 7 events in a total of 48,509 patients treated. However, all 7 events occurred in previously unexposed patients after first or second exposure to the drug, yielding a slightly greater true incidence of 0.035%. The lower figure reported in this study compared with the 2 studies using chart review probably reflects the decision to study only the incidence of AE requiring in-center use of resuscitative medication.[176] Of interest, the prevalence of suspected hypersensitivity in that study matched the findings of the previous retrospective reviews: 0.69% of prevalent patients were recorded as sensitive to iron dextran.

Pharmacovigilance surveillance studies yield information on deaths potentially related to IV iron. Deaths thought to be IV iron–related have been reported to the FDA for each of the IV iron agents available in the United States. In an analysis of US and European surveillance databases, 31 deaths occurring in association with 196 cases of iron dextran anaphylaxis were recorded in the United States between 1976 and 1996 compared with none with similar exposure rates with sodium ferric gluconate.[180] Another group studied the FDA Freedom of Information surveillance database to compare severe AE rates for IV iron drugs.[181] They confirmed higher anaphylaxis and fatality event rates for iron dextran than for the nondextran irons. These results should be interpreted with caution given that AEs for drugs in the marketing phase probably are grossly underreported for all agents; definitions for AEs are not generally accepted, as we have noted; and the primary intention of the database is to generate

signals of unexpected AEs, not to compare drugs.[182] Nonetheless, these results add to the body of evidence indicating a trend toward more frequent and more severe reactions with iron dextran.

Taking the pharmacovigilance information together with evidence that iron dextran AEs may occur in patients who have successfully received a previous test dose or series of therapeutic doses, we recommend that resuscitative medication and personnel trained to evaluate and resuscitate anaphylaxis accompany each administration of iron dextran.

## LIMITATIONS

### *Targets of Iron Therapy*

There are a number of serious limitations to the evidence supporting iron status targets. ESA dose and Hb level response as surrogates for iron efficacy are universal among iron intervention trials (IV iron challenge studies), RCTs, and uncontrolled prospective trials. No iron treatment trials have been designed or are sufficiently powered to yield information on outcomes, including the crucial issue of safety, that are directly important to patients. Of the 2 available RCTs comparing iron status targets, 1 used TSAT targets,[108] 1 used ferritin targets,[149] both were small, neither examined safety, and the TSAT trial showed increasing non–steady-state ferritin levels in the higher TSAT target arm. Conversely, IV iron challenge studies yield information that is limited to the acute hematologic response to a dose of IV iron—results that bear little relevance to optimum treatment targets for ongoing iron administration. Moreover, even when limited to predicting the acute response to IV iron challenge, available iron status tests perform poorly, yielding relatively low sensitivity and specificity over a range of cutoff values, flat receiver-operator characteristic curves, and low area under the curve. Finally, although stainable bone marrow iron may yield important information on the likelihood of storage iron depletion or iron excess or on the relationship between iron stores and results of serum iron status tests, the relevance of this information to setting optimum treatment targets for iron status is uncertain. In short, iron status targets as goals for treatment require treat-to-target RCTs to provide comparative evidence of efficacy and safety. However, available evidence is of limited quality or is altogether lacking.

### *Upper Level of Ferritin*

The limitations of available evidence, described previously, provide the rationale for the cautious use of IV iron at high ferritin levels.

### *Route of Administration*

In patients with HD-CKD, available RCTs are small, thereby limiting their potential applicability to unselected HD-CKD target populations. As in all IV iron studies to date, outcomes are limited to the surrogate Hb levels and ESA doses. Although these outcomes have financial implications for the total cost of anemia management, the comparative cost of anemia management using IV versus oral iron treatment has not been examined, and the relationship, if any, between surrogate outcomes and outcomes that are important to patients has not been determined. Moreover, although managing anemia requires chronic and ongoing care, most clinical trials involving therapeutic iron intervention are of relatively short duration; thus, the long-term effects of iron therapy remain unknown. Resolution of these issues, particularly in the ND-CKD and PD-CKD patient population, clearly is needed before a conclusive assessment of net benefit can be made.

### *Other Limitations*

1. Absence of generally accepted criteria for identifying IV iron–related AEs.
2. Absence of a distinction in the literature between reactions caused by labile iron and those caused by hypersensitivity.
3. No adequately-powered trials directly comparing different IV iron agents.

## CLINICAL IMPLICATIONS

AEs thought to be related to labile iron require a decrease in the dose or rate of infusion or both. AEs thought to be related to hypersensitivity to the agent require stopping the agent and preclude further administration.

# CPG AND CPR 3.3. USING PHARMACOLOGICAL AND NONPHARMACOLOGICAL ADJUVANTS TO ESA TREATMENT IN HD-CKD

Several pharmacological agents and nonpharmacological manipulations of the HD prescription have been examined for potential efficacy as adjuvants to ESA treatment. Studies are not available to address the use of pharmacological or nonpharmacological adjuvants to ESA treatment in patients with ND-CKD and PD-CKD.

**3.3.1 L-Carnitine: In the opinion of the Work Group, there is insufficient evidence to recommend the use of L-carnitine in the management of anemia in patients with CKD.**

**3.3.2 Vitamin C: In the opinion of the Work Group, there is insufficient evidence to recommend the use of vitamin C (ascorbate) in the management of anemia in patients with CKD.**

**3.3.3 Androgens: Androgens should not be used as an adjuvant to ESA treatment in anemic patients with CKD. *(STRONG RECOMMENDATION)***

## BACKGROUND

For the purposes of these recommendations, we consider adjuvants to ESA therapy to be therapeutic agents or approaches that aim to enhance responsiveness to ESA therapy in iron-replete patients. The target patient population may include both ESA-hyporesponsive and relatively responsive patients, although the focus of interest often is the hyporesponsive patient. A positive response to an adjuvant treatment consists of either an increase in Hb level at a given ESA dose or the attainment and maintenance of a specific Hb level at a lower ESA dose (see Executive Summary).

## RATIONALE

### *L-Carnitine*

*In the opinion of the Work Group, there is insufficient evidence of efficacy to recommend use of L-carnitine in the management of anemia in patients with CKD.* The role of carnitine deficiency in the pathogenesis of the anemia of CKD, if any, is unclear. Levocarnitine (L-carnitine) is a carrier molecule involved in the transport of long-chain fatty acids into the mitochondria, where they are oxidized to produce energy. L-carnitine is also thought to be involved in the metabolic conversion of acyl coenzyme A, which accumulates in patients with renal failure and is toxic to cells, to the less toxic acyl carnitine.[191] Deficiency of carnitine in patients on maintenance HD therapy was demonstrated nearly 30 years ago.[192] L-carnitine, which has been studied primarily when administered IV to HD patients, has been postulated to have beneficial effects on ESA-hyporesponsive anemia, HD-related hypotension, myocardial dysfunction, impaired exercise tolerance and performance status, muscle symptoms, and impaired nutritional status. However, no pathogenic mechanism by which carnitine deficiency might contribute to anemia or provoke ESA hyporesponsiveness has been conclusively elucidated. Furthermore, the therapeutic mechanism by which L-carnitine administration might improve anemia or enhance ESA responsiveness has not been determined. Finally, no consistent relationship between baseline plasma carnitine levels, anemia, and response to L-carnitine administration has been demonstrated.[193,194]

In considering L-carnitine administration, the Work Group confined evaluation of efficacy outcomes to RCTs in which the effect of IV L-carnitine on Hb level and ESA dosing had been reported in patients with CKD. Thus, Work Group conclusions and the resulting guideline statement 3.3.1 address the limited use of L-carnitine as an ESA adjuvant in patients with CKD. Guideline 3.3.1 does not address use of L-carnitine for potential nonhematologic indications.

In the United States, Medicare coverage for L-carnitine is available for patients who have been on dialysis therapy for at least 3 months, have a plasma free carnitine level less than 40 $\mu$mol/L, and have "erythropoietin-resistant anemia . . . that has not responded to standard erythropoietin dosage . . . and for which other causes have been investigated and adequately treated."[195] Hyporesponsiveness to ESAs is not specifically defined other than having a persistent Hct less than 30% despite erythropoietin dosage that "is considered clinically appropriate to treat the particular patient."

**Table 32. RCTs Evaluating Effects of Treatment with IV L-Carnitine on Hb Levels and ESA Doses in the HD-CKD Population**

| Author, Year | N | Follow-up (mo) | Applicability | Baseline | | | | Cointervention | Intervention [a] | Outcomes [b] | Result/ Metric | Comparison | | Result/ Metric | Comparison | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Hb (g/dL) | TSAT (%) | Ferritin (ng/mL) | ESA (IU/wk) | Description of Cointervention** | Arm 1<br>Arm 2 | Definition of Clinical Outcomes | Hb (g/dL) | Within Arm vs. Baseline | Between Arms | ESA (IU/wk) | Within Arm vs. Baseline | Between Arms | |
| Labonia, 1995 [199] | 13 | 6 | ↑↑ | 9.9 | nd | 232 | 5,615 | ESA adjusted; IV and/or oral iron adjusted [c] | L-Carnitine 1 g | Mean Hb<br>Mean ESA dose | 9.7 | NS | nd | 3,539 | ↓ | nd | ○ |
| | 11 | | | 9.8 | nd | 292 | 4,909 | | Placebo | | 9.3 | ↓ | | 4,909 | NS | | |
| Kletzmayer, 1999 [197] | 20 | 8 | ↑↑ | 10.5 [d] | 17 | 632 | 172.0 IU/kg/wk | ESA adjusted [e]; IV iron (20 mg iron saccharate at each HD treatment) given for first 4 mo then discontinued for additional 4 mo | L-Carnitine 5 mg/kg [N = 15] or 25 mg/kg [N = 5] | ESA dose at 4 mo [f] | 11.0 [d] | NS | nd | 152.3 IU/kg/wk | NS | NS | ○ |
| | 20 | | | 10.6 [d] | 16 | 606 | 143.9 IU/kg/wk | | Placebo | | 11.0 [d] | NS | | 158.6 IU/kg/wk | NS | | |
| Caruso, 1998 [196] | 15 | 6 | ↑↑ | 11.0 | nd | nd | 4,833 IU | ESA adjusted [g] | L-Carnitine 1 g | Mean Hb [h]<br>Mean ESA dose | 11.1 | NS | nd | 5,167 IU | NS | nd | ○ |
| | 16 | | | 10.9 | nd | nd | 5,875 IU | | Placebo | | 10.3 | NS | | 5,875 IU | NS | | |
| Vaux,* 2004 [200] | 13 | 4 | ↑↑ | 11.5 | nd | nd | 6,154 | ESA adjusted [i] | L-Carnitine 20 mg/kg | Δ Hb*<br>Δ ESA dose* | −0.08 | NS | nd | −769 | NS | nd | ○ |
| | 13 | | | 12.0 | nd | nd | 6,385 | | Placebo | | −0.26 | NS | | +153 | NS | | |
| Steiber,[200k] 2006 | 15 | 6 | ↑ | 11.3 | nd | nd | 57.8 (IU/kg/wk) | nd | L-Carnitine 20 mg/kg | Mean Δ ERI from baseline [l] | 11.9 | nd | nd | −1.6 [l] | nd | ✚ | ○ |
| | 19 | | | 11.5 | nd | nd | 52.5 (IU/kg/wk) | | Placebo | | 12.3 | nd | | +1.33 [l] | nd | | |
| Semeniuk,* 2000 [198] (Crossover) | 8 | 3 [j] | ↑ | 11.3 | 29 | 512 | 8,563 | ESA unadjusted; iron adjusted [k] | L-Carnitine 20 mg/kg | Mean Hb*<br>Mean ESA dose after 12 wk* | 11.5 | NS | nd | 8,750 | NS | nd | ○ |
| | 8 | | | 11.7 | | | 8,750 | | Placebo | | 11.9 | NS | | 9,133 | NS | | |

**Footnotes:**
* Not primarily an ESA/anemia study.
** Theoretically, adjusting the ESA dose will make any subsequent change in Hb irrelevant since Hb change is a likely response to an adjustment in ESA.
a. Intervention administered 3 times a week or at each HD session unless otherwise noted.
b. Primary outcome of study unless otherwise noted.
c. ESA adjusted weekly to maintain target Hb 9.3-11 g/dL; ferrous sulfate 3 times a day or IV iron dextran 100 mg 2-3 times a week to maintain TSAT >20%, ferritin >100 ng/mL, and serum iron >70 µg/dL; iron parameter measured monthly.
d. Data estimated from figure.
e. All patients were on a stable ESA dose at baseline, ESA treatment at each HD session. ESA dose adjusted if ΔHb ≥1 g/dL.
f. Results at 8 months were as follows: Hb for Arm 1 and Arm 2 was 10.5 g/dL as estimated from figure (NS); ESA dose at 8 months was 180.7 U/kg/wk for Arm 1 and 172.6 U/kg/wk for Arm 2 (between arm comparison and within group comparison at week 8 vs. week 4, NS).
g. Unclear if there was any cointervention with Iron. ESA protocol not documented.
h. ESA dose and Hb after additional 3-month follow-up period with no treatment was 6,364 IU and 11.0 g/dL in Arm 1 and 7,125 IU and 10.0 g/dL in Arm 2. The ESA dose in the placebo group was statistically significantly greater than at 6 months in that group. The between-group comparison at 6 months was NS.
i. Does not specify that all patients are on ESA; protocol not documented. Use of iron therapy not documented.
j. 12 weeks of drug/placebo → 6 week washout → crossover for 12 weeks.
k. No protocol data. Mean weekly ESA units remained constant throughout study, iron therapy was adjusted in 2 Treatment and 4 Control patients.
l. ERI: Erythropoietin resistance index, given in units erythropoietin dry weight$^{-1}$ [Hb]$^{-1}$.

**Coding of Outcomes:**
⬇ Statistically significant decrease from baseline; ✚ Statistically significant benefit to patient between Arm 1 vs. Arm 2.

The statement *There is insufficient evidence to recommend use of L-carnitine in the management of anemia in patients with CKD* is supported by results from 6 available RCTs of IV L-carnitine administration to ESA-treated HD patients (Table 32).[196-200] No RCTs are available in patients with PD-CKD or ND-CKD (Table 32). Anemia was the primary study outcome in only 3 of these studies.[196-198] No available RCTs were judged to be of high quality. Five of the 6 RCTs were judged to be of low quality. The RCTs were characterized by small numbers of enrolled patients, short duration of observation, concomitant use of IV and oral iron, adjustments in ESA dosage, high dropout rates, and uncertainty about specific ESA and/or iron dosing during the study. Between-group comparison, the result least subject to bias, was available in only 2 studies; there was no difference in either Hb level or ESA dose outcomes in 1 of these studies, and in the other, the comparison was only of erythropoietin resistance index (ERI). Serious limitations in method quality, important inconsistencies, major uncertainty about the directness and applicability of results, imprecise data, and a probability of bias rendered the overall quality of evidence very low (Table 33). None of the studies specifically enrolled patients with anemia and ESA hyporesponsiveness or identified a specific subset of patients particularly likely to respond to L-carnitine administration. Therefore, whether L-carnitine enhances the effect of ESA therapy in such patients is not known. The Work Group found no specific evidence of adverse drug effects associated with IV L-carnitine in patients with CKD. The absence of high-quality evidence for efficacy and safety supports the opinion of the Work Group that *there is insufficient evidence to recommend use of L-carnitine in the management of anemia in patients with CKD.*

The conclusion of the Work Group differs from those of selected previous reports. A meta-analysis concluded that L-carnitine administration was associated with higher Hb levels and

**Table 33. Use of L-Carnitine as an Adjuvant to ESA Treatment in the HD-CKD Population**

| Outcome | No. of Studies & Study Design | Total N | Methodological Quality of Studies[a] | Consistency | Directness of Evidence, including Applicability | Other Considerations | Summary of Findings: Quality of Evidence for Outcome | Summary of Findings: Qualitative Description of Effect Size | Importance of Outcome |
|---|---|---|---|---|---|---|---|---|---|
| Hb/Hct Level/ ESA Dose | 6 RCTs | 171 | Serious limitations[b] | Important inconsistencies[c] | Major uncertainty[d] | Imprecise data Probability of bias[e] | Very low | Uncertain benefit due to limited evidence. 1 study with between-arm comparison with partial evidence of reduced ESA dose. | Moderate |
| AEs | CKD population: 6 RCTs | 171 | | | | No significant AEs reported | | | High |
| Balance of Benefit and Harm: No Net Benefit | | | | | | | Quality of Overall Evidence: Very Low for Benefit | | |

Footnotes:
a. Theoretically, adjusting the ESA dose will make any subsequent change in Hb irrelevant since Hb change is a likely response to an adjustment in ESA.
b. Quality varied from Grade B to C.
c. N/A given between-group comparison was available in only 2 of 6 and only 1 showed statistically significant reduction in ESA dose.
d. The RCTs were characterized by small numbers of enrolled patients, short duration of observation, concomitant use of IV and oral iron, and adjustments in ESA dosage; 2 studies have primary outcomes other than Hb/Hct or ESA dose.
e. At least 3 studies sponsored by pharmaceutical companies (1 unstated).

lower ESA doses in ESA-treated patients with HD-CKD.[201] However, the meta-analysis included only 3 of the 6 RCTs examined by the Work Group and incorporated results from studies outlined in 3 abstracts, but that were never published in peer-reviewed journals. An NKF Carnitine Consensus Conference recommended the use of IV L-carnitine in selected ESA-hyporesponsive dialysis patients.[202] However, the consensus conference lacked systematic data abstraction and analysis of method quality.

Previous guideline development processes using systematic evidence review and rigorous evaluation for method quality have reached conclusions consistent with the current guideline statement, *there is insufficient evidence to recommend the use of L-carnitine in the management of anemia in patients with CKD*. These include NKF-KDOQI Guidelines for Nutrition in CKD,[203] previous NKF-KDOQI anemia guidelines,[2] and the Revised EBPGs for Anemia in CKD.[16]

Finally, although oral L-carnitine has also been studied as an ESA adjuvant, no RCTs are available. Direct comparison of IV to oral L-carnitine has not been reported in HD or other CKD patients.

### *Vitamin C (Ascorbate)*

*In the opinion of the Work Group, there is insufficient evidence to recommend use of vitamin C (ascorbate) in the management of anemia in patients with CKD.* Vitamin C has been reported to increase the release of iron from ferritin and the reticuloendothelial system and increase iron utilization during heme synthesis.[204,205] Although many HD patients may have plasma ascorbic acid levels less than the normal range,[206,207] whether this reflects a clinically significant deficiency is uncertain; in other studies, ascorbic acid levels have been normal or elevated.[208] It has been suggested that 150 to 200 mg of vitamin C daily is needed to normalize vitamin C levels in most HD patients.[206]

Several anecdotal reports, small case series,[194,209] and nonrandomized studies (primarily in HD patients with iron overload, elevated serum ferritin levels, and functional iron deficiency) using IV vitamin C in doses of 100 to 500 mg 3 times weekly have suggested a possible beneficial effect.[210-213] Plasma levels of ascorbic acid were not measured in most of the studies in which vitamin C was administered as an adjuvant to ESA therapy.

Four RCTs of vitamin C in ESA-treated HD patients have been reported (Table 34). Although the uncontrolled studies mentioned tended to focus on a possible role of IV vitamin C in patients with HD-CKD with iron overload and functional iron deficiency, only 1 RCT included patients with functional iron deficiency.[214] One RCT included patients with iatrogenic iron overload.[215] None of the studies specifically included patients with ESA hyporesponsiveness. These studies have not shown consistent benefit of IV vitamin C in either within-group or between-group comparisons.

Oral vitamin C, which can augment absorption of iron from the GI tract, has been evaluated as an adjunct to ESA therapy in small uncontrolled studies.[216-218] Oral and IV vitamin C were compared in 1 recent RCT in a small number of HD patients for 8 weeks; in a larger number of patients, oral vitamin C or no treatment were compared for 3 months.[219] There was

**Table 34. RCTs Evaluating Effects of Treatment with IV Ascorbic Acid on Hb Levels and ESA Doses in the HD-CKD Population**

| Author, Year | N | Follow-up (mo) | Applicability | Baseline Hb (g/dL) | Baseline TSAT (%) | Baseline Ferritin (ng/mL) | Baseline ESA (IU/wk) | Cointervention Description* | Intervention[a] Arm 1 / Arm 2 | Outcomes[b] Definition of Clinical Outcomes | Result/Metric Hb (g/dL) | Comparison Within Arm vs. Baseline | Comparison Between Arms | Result / Metric ESA (IU/wk) | Comparison Within Arm vs. Baseline | Comparison Between Arms | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *RCTs* | | | | | | | | | | | | | | | | | |
| Taji, 2004 [257] | 30 | 6 | ↑↑ | 10.5 | 30 | 379 | 4,400 | ESA adjusted; IV iron adjusted[d] | Ascorbic acid 100 mg | Mean Hb Mean ESA dose | 10.5 | nd | NS | 5,022[c] | NS | NS | ○ |
| | 31 | | | 10.7 | 34 | 331 | 4,645 | | Control | | 10.9 | nd | | 4,034[c] | NS | | |
| Deira, 2003 [215] | 9 | 6 | ↑ | 12.3 | 44 | 1,300 | 72.6 IU/kg/wk | ESA unadjusted first 3 mo[e] | Ascorbic acid 200 mg | Mean Hb Mean ESA dose[f] | 12.3 | NS | nd | 56.7 IU/kg/wk | NS | nd | ○ |
| | 9 | | | 12.0 | 44 | 1,104 | 46.9 IU/kg/wk | | Control | | 11.7 | NS | | 44.4 IU/kg/wk | NS | | |
| *RCT (crossovers) analyzed as cohort. Data presented for Arm 1 (Ascorbic acid → placebo/control) and Arm 2 (Placebo/control → Ascorbic acid). Results coded as comparison of baseline to end-of study findings within a study arm [g]* | | | | | | | | | | | | | | | | | |
| Keven, 2003 [256] | 30 | 6 | ↑↑ | 9.7 | 28 | 382 | 8,567 | SC ESA adjusted; IV iron unadjusted[h] | Ascorbic acid 500 mg | Mean Hb Mean ESA dose | 11.4 | ↑ | nd | 7,200 | ↓ | nd | ● |
| | | | | 11.4 | 39 | 381 | 7200 | | Placebo | | 11.1 | NS | | 7,800 | NS | | |
| | | | | 10.3 | 30 | 259 | 6,967 | | Placebo | | 11.0 | NS | | 7,667 | NS | | |
| | 30 | | | 11.0 | 32 | 263 | 7,667 | | Ascorbic acid 500 mg | | 12.2 | ↑ | nd | 6,679 | NS | nd | |
| Giancaspro, 2000 [214] | 12 | 3 | ↑↑ | 9.2 | 18 | 572 | 131[i] IU/kg/wk | ESA unadjusted[i] | Ascorbic acid 500 mg | Mean Hb | 10.0 | ↑ | nd | — | — | — | ○ |
| | | | | 10.0 | 26 | 398 | | | Control | | 8.9 | ↓ | | — | — | | |
| | | | | 9.1 | 18 | 484 | 145[g] IU/kg/wk | | Control | | 9.0 | NS | nd | — | — | — | |
| | 12 | | | 9.0 | 18 | 450 | | | Ascorbic acid 500 mg | | 9.9 | ↑ | | — | — | | |

**Footnotes:**
* Theoretically, adjusting the ESA dose will make any subsequent change in Hb irrelevant since Hb change is a likely response to an adjustment in ESA.
a. Intervention administered 3 times a week or at each HD session unless otherwise noted.
b. Primary outcome of study unless otherwise noted.
c. Data requested from study authors. Values given only for those patients who completed the study.
d. ESA dose adjusted according to a protocol, route of administration not documented. Iron was given to target ferritin >100 µg/L and <700 µg/L.
e. ESA dose unchanged during first 3 months, then adjusted during last 3 months to reach Hb levels similar to the baseline values. Iron treatment stopped at time of randomization except in 3 patients (1 in ascorbic acid group and 2 in control group) in whom it had already been discontinued 3 months before the study began.
f. Calcul ated ESA resistive index [weekly ESA dose (IU/kg/Wk) / Hb (g/dL) ] was also NS between the 2 arms.
g. In crossover trials, follow-up time given in months per treatment arm, not the total duration of study.
h. SC ESA 3 times a week at HD to target Hb of 11-12 g/dL, 100mg IV ferric sucrose twice a month. If ferritin ≥800 ng/mL, dose held and reduced by half once ferritin <800 ng/mL.
i. ESA aimed to maintain Hb target 12 g/dL but ESA dose unchanged during study. Route of administration not documented.
j. Iron therapy given if ferritin fell <100 µg/L, and patient was excluded from analysis.

**Coding of Outcomes:**
↑ Statistically significant increase from baseline; ↓ Statistically significant decrease from baseline.

no significant difference within or between groups in Hb levels or ESA doses in either comparison.

The long-term safety of IV ascorbic acid in HD patients remains undefined, with secondary oxalosis being the primary concern,[220,221] although this was not described with short-term use in any of the studies described. Plasma oxalate levels increase with IV vitamin C administration. A risk for calcium oxalate supersaturation in plasma recently was reported in HD patients administered IV vitamin C.[222] Aside from the potential for systemic oxalosis, concern is also warranted because a pro-oxidant effect of high-dose vitamin C, either directly or through its effects on mobilization of iron, has been reported.[223,224]

In summary, the Work Group concluded that serious method limitations and important inconsistencies render the quality of available information on vitamin C efficacy very low (Table 35). At the same time, information on the potential serious adverse effects (oxalosis) of chronic vitamin C administration is altogether lacking. Thus, the Work Group concluded that *there is insufficient evidence to recommend use of vitamin C (ascorbate) in the management of anemia in*

**Table 35. Use of Ascorbic Acid as an Adjuvant to ESA Treatment in the HD-CKD Population**

| Outcome | No. of Studies & Study Design | Total N | Methodological Quality of Studies[a] | Consistency | Directness of Evidence including Applicability | Other Considerations | Summary of Findings: Quality of Evidence for Outcome | Summary of Findings: Qualitative Description of Effect Size | Importance of Outcome |
|---|---|---|---|---|---|---|---|---|---|
| Hb/Hct Level/ ESA Dose | 4 RCTs | 154 | Serious limitations[b] | Important inconsistencies[c] | Direct | Imprecise data[d] Sparse data | Very low | No consistent benefit. 2 of 4 reports (both crossover studies) showed benefit for Hb/Hct; 1 of 4 showed benefit for ESA. | Moderate |
| AEs | CKD population: 4 RCTs<br>General population: observational data | 154+ | None described in RCTs. Theoretical concern given isolated rare reports of toxicity in patients with ARF or CKD, including secondary systemic oxalosis, retinal oxalosis, calcium oxalate arthopathy, myocardial calcium oxalate deposition. Toxicity in general population with intermittent IV doses as used in HD-CKD studies is not known nor is applicability to HD-CKD. | | | | | | High |
| Balance of Benefit and Harm: No Net Benefit | | | | | | | Quality of Overall Evidence: Very Low for Benefit | | |

Footnotes:
a. Theoretically, adjusting the ESA dose will make any subsequent change in Hb irrelevant since Hb change is a likely response to an adjustment in ESA.
b. 1 Grade B and 3 Grade C studies.
c. Inconsistencies with regard to the direction of the results for treatment and placebo/control groups.
d. References for statistical comparisons varied between studies (within arm or between arms).

**Table 36. RCTs Evaluating Effects of Treatment With IM Androgens on Hb Levels in the HD-CKD Population**

| Author, Year | N | Follow-up (mo) | Applicability | Baseline: Hb (g/dL) | Baseline: TSAT (%) | Baseline: Ferritin (ng/mL) | Cointervention: Description of Cointervention | Intervention: Arm 1 / Arm 2 | Outcomes[a]: Definition of Clinical Outcomes | Result/Metric: Hb (g/dL) | Comparison: Within Arm vs. Baseline | Comparison: Between Arms | AEs: Description of Event | AEs: D/C of Drug or Reduction in Dose | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sheashaa, 2005 [259] | 16 | 6 | ↑↑ | 7.5 | 34 | 403 | SC ESA[b] 1,000 IU TIW; IV iron protocol nd | Nandrolone decanoate 50 mg IM 2x/wk | Mean Hb at 6 mo | 10.4 | ↑ | NS | Transient flu-like symptoms, distressing hirsutism, and/or elevated liver function tests | 4[c] | ⊙ |
| | 16 | | | 7.3 | 35 | 394 | | Control | | 10.0 | ↑ | | | 0 | |
| Gaughan, 1997 [260] | 9 | 6 | ↑↑ | 8.4 | 41 | 364 | IV ESA 1,500 IU TIW [d]; Oral and/or IV iron adjusted [e] | Nandrolone decanoate-100 mg IM weekly | Mean Hb at 26 wk | 11.0 | ↑ | + | Mild side effects attributed to nandrolone decanoate: Acne N = 1, injection site pain N = 2, and injection site hematoma N = 1. Significant ↑ in serum glutamic oxaloacetic transaminase from baseline in androgen group | 0 | ○ |
| | 10 | | | 8.3 | 32 | 301 | | Control | | 9.4 | ↑ | | | 0 | |
| Berns, 1992 [261] | 6 | 4 | ↑ | 7.8 | nd | 1,322 | IV ESA[b] 40 IU/kg TIW; Oral and/or IV iron adjusted [e] | Nandrolone decanoate 2 mg/kg IM weekly[f] | Rate of increase in Hb | 0.12/wk | nd | NS | Unacceptable acne | 0 | ○ |
| | 6 | | | 7.8 | nd | 776 | | Control | | 0.11/wk | nd | | | 2 | |

Footnotes:
a. Primary outcome of study unless otherwise noted.
b. All ESA administered per study protocol at start; none with prior ESA treatment.
c. Subsequent improvement in symptoms after discontinuation of drug.
d. Per study protocol at start; washout until Hb 8.7g/dL in those previously on ESA.
e. Iron adjusted to maintain ferritin ≥100 mg/dL and TSAT ≥20%.
f. Patients randomized to nandrolone decanoate received nandrolone for 2 months before starting ESA.

Coding of Outcomes:
+ Statistically significant benefit for arm 1 vs. arm 2 (with reference to benefit to patient)
↑ Statistically significant increase from baseline

*patients with CKD.* None of the RCTs enrolled patients with ESA hyporesponsiveness, and only 1 enrolled patients with functional iron deficiency[214]; therefore, whether IV vitamin C enhances the effect of ESA therapy or iron metabolism in such patients is not known.

In addition to the lack of definitive evidence of efficacy and safety, there is no evidence that clinical outcomes—such as reduced hospitalizations, improved cardiovascular status, and reduced mortality—are improved in patients for whom IV vitamin C treatment is initiated as an ESA adjuvant. Whereas the putative mechanism of action of IV vitamin C as an ESA adjuvant is an increase in the release of iron from ferritin and the reticuloendothelial system and increased iron utilization during heme synthesis, none of the studies reviewed showed reduced utilization of administered iron therapy. IV vitamin C has not been evaluated in patients with PD-CKD.

Therefore, given the low quality of evidence for efficacy and unresolved concerns for serious AEs of chronic administration, the Work Group concluded that *there is insufficient evidence to recommend use of vitamin C (ascorbate) in the management of anemia in patients with CKD.*

### *Androgens*

*Androgens should not be used as an adjuvant to ESA treatment in anemic patients with CKD.* Before the availability of epoetin therapy, androgens were used regularly in the treatment of anemia in dialysis patients despite the need for intramuscular (IM) injection and a variety of AEs, including acne, virilization, priapism, liver dysfunction, injection-site pain, and risk for peliosis hepatis and hepatocellular carcinoma. Proposed mechanisms of action of these drugs include increased erythropoietin production from renal or nonrenal sites, increased sensitivity of erythroid progenitors to the effects of erythropoietin, and increased red blood cell survival.

Three RCTs explored a possible role for androgens in combination with ESA therapy in HD patients (Table 36). All were small short-term studies, currently recommended Hb levels were not achieved, and in 2 of the studies, the ESA doses used were lower than those used in most patients with HD-CKD on chronic ESA treatment. The studies did not enroll patients with ESA hyporesponsiveness, so it is not known what effect, if any, androgens would have in such patients. It is unclear whether any enhanced erythropoietic effect caused by androgens would confer clinical benefits that outweigh the potentially significant AEs of androgens or the effects of simply allowing patients to remain at somewhat lower Hb levels without androgens. Short-term and long-term toxicity of androgens limit their use, especially in women.

In short, evidence for efficacy of androgens is characterized by serious method limitations, important inconsistencies, and sparse data (Table 37).

**Table 37. Use of Androgens as an Adjuvant to ESA Treatment in the HD-CKD Population**

| Outcome | No. of Studies & Study Design | Total N | Methodological Quality of Studies | Consistency | Directness of Evidence including Applicability | Other Considerations | Summary of Findings: Quality of Evidence for Outcome | Summary of Findings: Qualitative Description of Effect Size | Summary of Findings: Importance of Outcome |
|---|---|---|---|---|---|---|---|---|---|
| Hb/Hct Level/ ESA dose | 3 RCTs | 63 | Serious limitations[a] | Important inconsistencies[b] | Direct[c,d] | Sparse data | Very low | No consistent benefit. Only 1 of 3 papers showing significant between-arm comparison in Hb/Hct (difference in Hb of 1.6 g/dL).[c] | Moderate |
| AEs | CKD population: 3 RCTs<br>General population: trials, case reports, narrative reviews | 63+ | Mild to severe AEs noted in RCTs included severe acne, elevated AST, discomfort at injection site. This is consistent with reported AEs from androgens in non-CKD populations which include virilization, priapism, peliosis hepatis, liver enzyme abnormalities, and hepatocellular carcinoma. Mechanism of action and profile of AEs of androgens are believed to be similar in non-CKD and CKD populations. | | | | | | High |
| Balance of Benefit and Harm: No Net Benefit | | | | | | | Quality of Overall Evidence: Very Low for Benefit | | |

Footnotes:
a. 1 Grade B and 2 Grade C studies.
b. Statistically significant effect with only 1 of 3 studies.
c. The studies used different ESA and iron protocols and had different definitions for the Hb/Hct outcome.
d. The studies used different ESA and iron protocols and had different definitions for the Hb/Hct outcome.

The Work Group, as a result, considered the quality of evidence to be very low. The Work Group judged mild to severe drug-related AEs in the target and general population as being highly important. Given the very low quality of evidence for efficacy and demonstrated AEs of androgen therapy, the Work Group concluded that *androgens should not be used as an adjuvant to ESA treatment in anemic patients with CKD. (Strong Recommendation)*

### *Other Pharmacological Agents Not Addressed in Guideline Statements*

*Statins*

A growing body of literature indicates that there may be clinically important, non–lipid-lowering effects of the hydroxymethylglutaryl coenzyme A reductase inhibitors, or statins, including antiproliferative, anticoagulant, immunosuppressive, anti-inflammatory, antioxidant, and cytoprotective effects. Because a component of anemia in patients with CKD may be related to underlying inflammatory processes, a potential role for statins in enhancing epoetin therapy may be plausible. Only a single small retrospective study addressed statins as adjuvants to ESA therapy.[225] Given the nature of this study, further investigation of the effects of statins as ESA adjuvants may be warranted, but their utility, if any, remains to be determined.

*Pentoxifylline*

One small uncontrolled open-label study of 16 patients with CKD (HD, PD, and transplant recipients) with ESA-resistant anemia evaluated the effect of pentoxifylline as an ESA adjuvant.[226] Further studies may be warranted, but the utility, if any, of pentoxifylline as an adjuvant to ESA treatment in patients with HD-CKD remains to be determined.

*Vitamin Supplements Other Than Vitamin C*

Although deficiencies of vitamin $B_{12}$ and folate are recognized causes of anemia and rarely are the basis for ESA hyporesponsiveness, there are no RCTs showing that supplementation with vitamin $B_{12}$, folate, or other vitamins (in the absence of documented vitamin deficiency) is an effective adjuvant to ESA therapy. One RCT of ESA-treated HD patients did not find a benefit of pyridoxine (vitamin $B_6$) as an ESA adjuvant.[227]

### *Summary*

There was insufficient evidence for efficacy to recommend use of statins, pentoxifylline, and vitamin $B_{12}$ and folate supplements (other than when used to correct documented vitamin deficiency) as adjuvants to ESA therapy in patients with CKD. Because these therapies are not in widespread use as ESA adjuvants, they are presented here primarily for general information, but were not considered by the Anemia Work Group for inclusion in Guidelines or CPRs addressing ESA adjuvants.

### *Modifications of Dialysis Treatments Not Addressed in Guideline Statements*

The effects of modifications of the HD dialysis prescription and various components of the HD treatment on anemia in patients with HD-CKD have been studied. Unlike the pharmacological agents discussed, it is not likely that these dialysis treatment modifications would be undertaken for the primary purpose of enhancing ESA responsive-

ness, and they therefore were not considered by the Anemia Work Group for inclusion in Guidelines or CPRs addressing ESA adjuvants.

Distinguishing between the effects of increased HD dose (ie, urea reduction ratio [URR] or Kt/V) from effects of concomitant changes in membrane on response to ESA therapy is difficult because most studies compared different Kt/V levels using membranes of different types. The effects of dialysate composition, primarily in comparisons of standard bicarbonate dialysate to ultrapure dialysate, also have been evaluated. No RCTs have been reported that compared HD and PD (or different doses of PD) on anemia outcomes or ESA dose in ESA-treated patients.

*HD Intensity ("dose"), Membrane Type, and Other Dialysis Modifications*

A few studies have examined the relationship between dialysis dose and dialysis membrane type and anemia outcomes,[228-236] with conflicting results. Because in most of these studies, patients in the higher versus lower Kt/V (or URR) groups were dialyzed with membranes of different composition and flux, the role of dialysis dose cannot be separated from the effects of membrane permeability or biocompatibility. One of these studies, which was not an RCT, compared different levels of Kt/V with the same membranes[236] and observed an inverse correlation between ESA dose and Kt/V, but no relationship between Kt/V and Hb level, in HD patients treated with unsubstituted cellulose membranes. In a subsequent report, which also was not an RCT,[235] it was suggested that this relationship holds only for patients with a Kt/V less than 1.33, and above this level, there was no correlation between Kt/V and ESA dose.

Three RCTs were performed in HD patients in which anemia-related outcomes were compared for high-flux and low-flux dialyzers.[229-231] No difference in Hct or ESA responsiveness was found between groups. Assessment of these studies is complicated by the use of membranes of different composition, attainment of different Kt/V levels, short study duration, and inclusion of patients not on ESA therapy. In another RCT of HD patients who were unable to reach a target Hb level of 11 g/dL or greater with at least 200 U/kg/wk of recombinant human erythropoietin (rHuEPO), low-flux and high-flux polysulfone dialyzers were compared.[228] Kt/V values were similar in the 2 groups at baseline and the end of the 6-month study. Hb levels were higher and ESA doses were lower in the high-flux group by 3 months and remained so to the end of the study.

*Vitamin E*

Vitamin E has been considered as a potential adjuvant to ESA therapy based on the consideration that antioxidant properties of vitamin E may prolong red blood cell life span in patients with CKD and anemia. Oral vitamin E has not been studied in prospective controlled trials of ESA-treated patients. Vitamin E–bonded dialyzers were studied in a single RCT in which the primary focus was the effects of a vitamin E–bonded hemodialyzer on carotid artery atherosclerosis and rheological properties of red blood cells.[237] Mean ESA dose decreased after 1 year on the vitamin E–bonded dialyzers, but Hb levels and other important parameters, such as amount of iron administered, were not reported. The safety of vitamin E also must be considered: a recent meta-analysis in the non–kidney-disease population suggested that doses of 400 U/d or more of vitamin E were associated with an increase in all-cause mortality.[238]

*Ultrapure Dialysate*

Inflammatory cytokines are proposed to interfere with the erythropoietic effect of ESAs both directly and through impaired mobilization and utilization of iron. An inflammatory stimulus in HD patients may be endotoxin or bacterial contamination of dialysate. Standards for bacterial and endotoxin content of water used for dialysis and for dialysate vary around the world. For dialysate, recently revised voluntary standards (Association for the Advancement of Medical Instrumentation) include an upper limit for bacteria of 200 CFU/mL, and for endotoxin, of 2 EU/mL.[239] In some countries, limits of 100 CFU/mL and 0.25 EU/mL for bacteria and endotoxin have been applied, respectively. Ultrapure dialysate has 0.1 CFU/mL or less of bacteria and less than 0.03 EU/mL of endotoxin.[239,240] Ultrapure dialysate is produced by generation of microbiologically purer water than used for standard dialysate, minimizing potentially contaminating biofilm, and use of ultrafilters. Some uncontrolled observations suggest that the re-

sponse to ESA treatment may be enhanced by the use of ultrapure dialysate solutions.[241] Three RCTs examined the effects of using online-produced or filtered ultrapure dialysate on anemia outcomes in HD patients.[242-244] ESA doses were significantly decreased by up to 33%. The use of ultrapure dialysate typically was associated with lower C-reactive protein and interleukin 6 levels compared with standard dialysate, thought to be indicative of reduced inflammatory responses.

*Hemodiafiltration*

Hemodiafiltration (HDF) has been evaluated prospectively in a few RCTs with conflicting results. A small randomized study that compared acetate-free biofiltration and low-flux HD in ESA-treated patients suggested that ESA doses were lower with HDF.[245] In a comparison of online HDF with high-flux HD, no differences in Hb levels or ESA dose were observed.[246] Another study, in which only about 40% of patients were being treated with an ESA, compared HDF and high-flux HD. It found no difference in Hb levels or ESA doses.[247] HDF with online production of pyrogen-free solutions also may have an advantage in terms or anemia outcomes compared with conventional solutions.[248]

*Daily and Nocturnal HD*

There are no RCTs comparing either daily HD or nocturnal HD with conventional intermittent HD for effects on anemia or ESA requirements. In the most recent report from a small nonrandomized comparison of short daily, long nocturnal, and conventional HD, only nocturnal HD patients had a statistically significant increase in Hb levels during 18 months; ESA doses also tended to increase, although the difference was not statistically significant.[249] In 1 study, conventional HD patients with a baseline single-pool Kt/V of at least 1.3 were changed to short-daily dialysis 6 times per week with the same weekly dialysis time.[250] Weekly Kt/V increased by 31%. In the patients studied for 12 months, mean ESA dose decreased 45% compared with baseline, with stable or increased Hb levels. Doses of ESA were trending upward between 6 and 12 months of observation. Other studies, none of which were RCTs, reported variable results.[251-254] To our knowledge, it has not been studied whether changing from conventional HD to daily or nocturnal HD specifically enhances ESA responsiveness in ESA-hyporesponsive patients.

*Peritoneal Dialysis*

Although observational data have suggested that patients treated with PD may have lower ESA requirements than HD patients,[255,256] no controlled trials have been reported comparing HD and PD or different doses of PD on anemia outcomes or ESA dose in ESA-treated patients.

***Summary***

Whereas the Anemia Work Group does not recommend changing patients with HD-CKD from standard bicarbonate dialysate to ultrapure dialysate for the purpose of enhancing ESA responsiveness, studies suggest that the use of ultrapure dialysate results in lower ESA doses in patients with HD-CKD. There is insufficient evidence at this time that other modifications in the HD prescription or various components of the HD treatment enhance ESA therapy.

## LIMITATIONS

We acknowledge the limitations of these guidelines. For lack of evidence, we do not address the potential adjuvant effect of pharmacological agents or alterations in dialysis prescription on anemia outcomes in patients without concomitant ESA therapy. Among patients receiving ESA therapy, available evidence is restricted to patients with HD-CKD. Among available ESA agents, evidence is restricted to use of epoetin alfa. As reported elsewhere in this document, a guideline needs to be based on both high- or moderate-quantity evidence and consistently demonstrated net medical benefit. Therefore, we considered appropriately designed, adequately powered RCTs to be the required foundation. Few such RCTs currently are available. Among available RCTs, only hematologic outcomes were assessed: no evidence exists to confirm the assumption that hematologic outcomes gained with adjuvant therapy share the same risk-benefit profile as those gained with ESA and iron therapy alone. Finally, although the primary motivation behind adjuvant therapy is to decrease cost by decreasing ESA doses, information on the comparative costs and benefits of ESA with and without proposed noniron adjuvants is lacking.

# CPR 3.4.: TRANSFUSION THERAPY

Red blood cell transfusions should be used judiciously in patients with CKD, especially because of the potential development of sensitivity affecting future kidney transplantation. However, despite the use of ESA and iron therapy, transfusion with red blood cells occasionally is required, in particular in the setting of acute bleeding.

**3.4.1 In the opinion of the Work Group, no single Hb concentration justifies or requires transfusion. In particular, the target Hb recommended for chronic anemia management (see Guideline 2.1) *should not serve as a transfusion trigger.***

## RATIONALE

Anemia commonly is observed in patients with CKD. The degree of anemia is a reflection of the severity of CKD. Anemia impacts on cardiac function and is associated with increased cardiovascular morbidity and mortality and decreased QOL.[262]

Typically, the anemia of CKD is chronic, and patients compensate for the anemia through a number of mechanisms. Thus, in determining the need for red blood cell transfusions, it is important to evaluate the state of compensation of the patient. In general, otherwise healthy individuals display few symptoms or signs of anemia at rest when Hb level is greater than 7 to 8 g/dL, although they may show dyspnea with exertion. At 6 g/dL, most patients will report some weakness and, with progressive decreases in Hb values, dyspnea at rest and congestive heart failure (CHF) occur.[263] Also, the risk for relevant tissue hypoxia increases, particularly in the presence of vascular disease. Therefore, in general, decisions concerning transfusion are not acute, and there is an opportunity to consider the risks and benefits of transfusion as treatment.

Before considering transfusion of red blood cells for the treatment of chronic anemia, it is essential to assess signs and symptoms and determine the cause of the anemia so that, when appropriate, treatment other than red blood cell transfusions may be used. Classic examples of anemias that may be severe, but correctible by alternative therapies, are iron-deficiency anemia and pernicious anemia in adults.

If red blood cell transfusions are deemed necessary for the immediate treatment of patients with chronic anemia, the goal should be to attain an Hb concentration that will prevent inadequate tissue oxygenation or cardiac failure. When red blood cell transfusions are considered for the long-term treatment of patients with chronic anemia, treatment goals (other than to maintain a certain Hb concentration) should be determined in advance and assessed serially to ascertain whether the goals are being met. In this setting, the physician and patient must consider such questions as: What symptoms and signs are caused or aggravated by the anemia? Can these symptoms and signs be alleviated by red blood cell transfusions? What is the minimum level of Hb at which the patient can function satisfactorily? Do the potential benefits of red blood cell transfusions outweigh the risks (and possibly the inconveniences) for any given patient? In determining the risk-benefit ratio for a given patient, such factors as lifestyle, the presence of other medical conditions, the likely duration of the anemia, and the patient's overall prognosis should be considered. For example, a patient may be willing to tolerate a very limited capacity for exertion if anemia is likely to be temporary, but not if the anemia will be permanent.

In general, risks per unit of red blood cells transfused are the same as in any setting. A number of retrospective studies have identified risks related to aggressive transfusion support. A review of patients with acute coronary artery syndromes revealed a greater mortality rate in transfusion recipients.[264] In the presence of severe chronic anemia, transfusion may lead to CHF, particularly in the elderly. In such cases, red blood cell transfusions must be administered very slowly, and, in patients with HD-CKD, transfusion during hemofiltration may be required. The administration of many red blood cell transfusions over a prolonged period can eventually lead to iron overload.

The use of ESAs can greatly reduce the need for red blood cell transfusions in patients with anemia of CKD when target Hb concentrations are reached and maintained.[265,266] With the advent of new immunosuppressant regimens after 1995, the benefits of pretransplantation transfusion have been

rendered largely obsolete. There is some evidence that donor-specific transfusion with living donor transplantation improves survival, but the decision to perform donor-specific transfusion must still be made on a case-by-case basis. Blood transfusions can induce antibodies to histocompatibility leukocyte antigens that can reduce the success of kidney transplantation; thus, transfusions generally should be avoided in patients awaiting a renal transplant.[267] If deemed essential, red blood cell transfusions in this patient group should be conducted in line with published recommendations.[268]

If therapy with an ESA is started at the Hb concentration recommended in these guidelines and Hb levels are maintained at the recommended target concentrations, blood transfusions should be necessary only for patients with acute bleeding (usually GI), acute hemolysis, or severe inflammation or blood loss through surgery, and then only in an emergency or if the patient exhibits a rapid decline in condition. International guidelines provide criteria for deciding when transfusion is necessary.[269-271]

Patients with CKD on HD therapy are more likely to need blood transfusions than those on PD therapy because of the HD procedure itself. Patients on HD therapy lose blood from frequent blood tests, trapped blood in the dialyzer and tubing,[272] and increased risk for GI bleeding from anticoagulants. However, aggressive iron replacement has largely eliminated the need for red blood cell transfusions, even for patients on HD therapy.

# CPR 3.5. EVALUATING AND CORRECTING PERSISTENT FAILURE TO REACH OR MAINTAIN INTENDED HB

Although relative resistance to the effect of ESAs is a common problem in managing the anemia of patients with CKD and is the subject of intense interest, the bulk of available information suggests that—in the absence of iron deficiency—there are few readily reversible factors that contribute to ESA hyporesponsiveness.

**3.5.1 Hyporesponse to ESA and iron therapy:**

**In the opinion of the Work Group, the patient with anemia and CKD should undergo evaluation for specific causes of hyporesponse whenever the Hb level is inappropriately low for the ESA dose administered. Such conditions include, but are not limited to:**

- **A significant increase in the ESA dose requirement to maintain a certain Hb level or a significant decrease in Hb level at a constant ESA dose.**
- **A failure to increase the Hb level to greater than 11 g/dL despite an ESA dose equivalent to epoetin greater than 500 IU/kg/wk.**

**3.5.2 Evaluation for PRCA:**

**In the opinion of the Work Group, evaluation for antibody-mediated PRCA should be undertaken when a patient receiving ESA therapy for more than 4 weeks develops each of the following:**

- **Sudden rapid decrease in Hb level at the rate of 0.5 to 1.0 g/dL/wk, *or* requirement of red blood cell transfusions at the rate of approximately 1 to 2 per week, *AND***
- **Normal platelet and white blood cell counts, *AND***
- **Absolute reticulocyte count less than 10,000/$\mu$L.**

## BACKGROUND

### *Hyporesponsiveness to ESAs*

Hyporesponsiveness to ESAs is a common finding of grave significance whether it is manifested by persistent, below-target Hb levels despite substantial ESA doses or by within-target Hb levels attained only at very high ESA doses. In patients with HD-CKD undergoing ESA therapy, Hb levels less than 11 g/dL are associated with increased mortality and hospitalization rates, and failure to achieve an Hb level greater than 11 g/dL is a poor prognostic sign. Given the disproportionate burden of morbidity and mortality that the hyporesponsive patient population bears and the ESA expense that hyporesponsiveness engenders, hyporesponsiveness to ESAs deserves more scrutiny than it has received. Although most disorders associated with hyporesponsiveness are readily apparent, a review of available information on patients with coexisting hematologic or oncological disorders may be worthwhile. Similarly, a rare disorder, PRCA, deserves special consideration.

### *Antibody-Mediated PRCA*

Rarely, patients undergoing ESA therapy develop antibodies that neutralize both ESA and endogenous erythropoietin. The resulting syndrome, antibody-mediated PRCA, is characterized by the sudden development of severe transfusion-dependent anemia. Rapid recognition, appropriate evaluation, and prompt intervention can be effective in limiting the consequences of this life-threatening hyporesponse condition.

Antibody-mediated PRCA, although rare in patients administered ESAs, received urgent attention after 1998. Between 1989 and 1998, three reports described the development of PRCA in a small number of patients with CKD administered ESAs.[273,274] Reports of PRCA increased sharply in 1998 and reached a peak in 2002 (Fig 17).[273,275] These reports were associated with SC administration of an epoetin alfa formulation not available in the United States. In 1998, in this formulation, polysorbate 80 was used to replace human albumin. Preparations of this product included single-dose syringes fitted with uncoated rubber stoppers and prefilled with epoetin alfa. Results of an intensive investigation indicate that in the presence of polysorbate 80 and

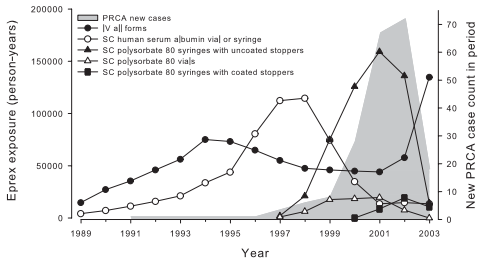


**Fig 17. Exposure to Eprex® and case counts of PRCA. Relationship between reporting rate of new cases of PRCA and route of administration (SC versus IV), stabilizer (human serum albumin versus polysorbate 80), and coated versus uncoated stoppers in preparations of Eprex®, a form of epoetin alfa marketed outside the United States. Reprinted with permission.[275]**

uncoated rubber can release organic compounds that may act as immunoadjuvants, thereby increasing the immunogenicity of SC-administered epoetin alfa.[273-275]

Between 2001 and late 2003, single-dose syringes with polysorbate 80 and uncoated stoppers were replaced by syringes with fluoro-resin-coated stoppers.[275] In addition, SC administration of the agent had been prohibited in Europe and discouraged in Canada. By 2004, the incidence of new antibody-mediated PRCA had decreased to pre-1998 levels.

Isolated cases of PRCA have been observed in association with the use of other ESAs.[273,274,276-279] No case of antibody-associated PRCA has been documented in patients treated with only IV administration of ESAs.[274] An increase in antibody-mediated PRCA has not been seen among patients in the United States, where the immunogenic formulation has not been available.

The incidence rate of PRCA in patients who were exposed to SC-administered ESA from syringes with uncoated stoppers and polysorbate 80 is estimated at 4.23 cases/10,000 patient-years.[275] The incidence with SC use of all other forms of SC-administered ESA is estimated to be 0.5 cases/10,000 patient-years.[275] The finding that antibody-mediated PRCA develops only rarely, even among patients exposed to adversely equipped syringes, suggests that additional factors must have been involved to render ESA immunogenic, potentially including differences in host immunoreactivity or product storage and handling.

## RATIONALE

### *Hyporesponse to ESA and Iron Therapy*

*The patient with anemia and CKD should undergo evaluation for specific causes of hyporesponse if Hb level is persistently less than 11 g/dL AND if ESA doses are equivalent to epoetin greater than 500 IU/kg/wk.* Results from the USRDS national data system show that the distribution of epoetin alfa doses is quite broad, the number of administrations per percentile range is relatively constant over the full spectrum of doses, and the relationship between percentile range and mean epoetin dose per administration is distinctly nonlinear (Fig 18). In these unselected patients, the 99th percentile doses are 30 times greater than the 1st percentile doses, and the top 20% of patients seem to be using a disproportionate amount of ESA compared with the lower 80%.

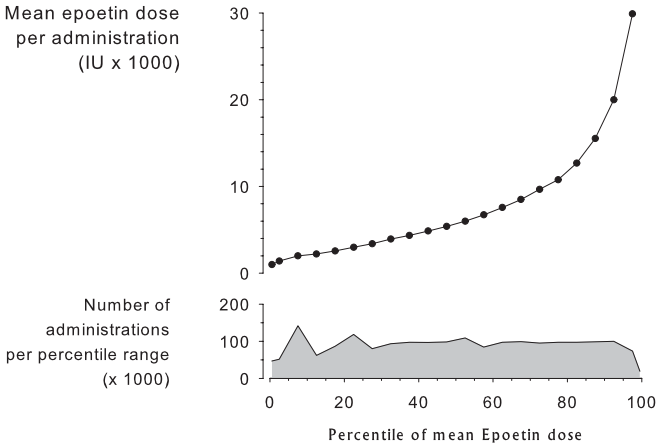


**Fig 18. Mean epoetin dose per patient per administration by percentile of dose (1st, 5th to 95th, and 99th). Data are for December 2004, courtesy of USRDS.**

Available information on hyporesponsiveness is weakened by the lack of a validated quantitative measure of ESA resistance. Although a resistance index—calculated by dividing the weight-adjusted ESA dose by Hb level—has been proposed, precisely how the ESA dose and Hb level should be determined (area under the curve, single value, time averaged) has not been standardized and reference values have not been validated.

Factors most commonly associated with persistent failure to achieve target Hb levels for at least 6 months despite ESA therapy include the following[280]:

- Persistent iron deficiency
- Frequent hospitalization
- Hospitalization for infection
- Temporary catheter insertion
- Permanent catheter insertion
- Hypoalbuminemia
- Elevated C-reactive protein level.

In general, these problems do not pose a diagnostic challenge or yield to simple solutions. A second set of disorders also may be identified among hyporesponsive patients. Unfortunately, they also are found among those who do not meet criteria for hyporesponsiveness, and they also represent neither frequent nor elusive diagnoses[280]:

- Pancytopenia/aplastic anemia
- Hemolytic anemia
- Chronic blood loss
- Cancer, chemotherapy, or radiotherapy
- Inflammatory disease
- Acquired immune deficiency syndrome
- Infection.

Only a small percentage of patients with a Hb level less than 11 g/dL fail to respond to ESA therapy. Persistency analysis shows that approximately 10% of patients with HD-CKD who enter a 6-month period with a Hb level less than 11 g/dL remain at less than that threshold for 6 consecutive months.[112] Among patients with a Hb level less than 11 g/dL administered high ESA doses (epoetin alfa $>$ 30,000 IU/wk), only 0.6% of patients remained at less than that threshold for 6 consecutive months.

In short, the available evidence suggests that approximately 20% of patients with HD-CKD in the United States are administered ESA doses in excess of an epoetin equivalent of 30,000 IU/wk, or 428 IU/kg/wk for a 70-kg patient (Fig 2). Approximately 10% of patients with an Hb level less than 11 g/dL will persistently fail to attain a target Hb level of 11 g/dL or greater. However, among US patients with an Hb level less than 11 g/dL and ESA doses in excess of 30,000 IU/wk epoetin equivalents, less than 1% will remain at less than the Hb target for 6 months.

The patient with anemia, CKD, and a preexisting hematologic disorder represents an uncommon, but challenging, cause of ESA hyporesponsiveness and deserves special consideration. The quality of reviewed material is insufficient to provide specific recommendations. However, a brief review of the available literature may prove helpful to medical decision making in the treatment of these patients.

Management of anemia in patients with CKD with preexisting hematologic disorders associated with anemia may present specific problems because of multifactorial causes. In some patients, anemia may result predominantly from low endogenous erythropoietin levels and can be corrected readily by administration of ESAs. In other disorders, impaired marrow function, ineffective erythropoiesis, and shortened red blood cell survival may contribute to anemia and ESA hyporesponsiveness.

We identified a small number of publications that evaluated ESA responsiveness in patients with CKD and preexisting hematologic disorders (Table 38). The publications are predominantly observational, taking the form of individual case reports or reports of a small series of patients. Although the available information is insufficient to support guidelines or CPRs, the following summary statements may be helpful:

*Thalassemia*

- Patients with thalassemia have a poor response to ESA.[281-283]
- Higher doses of ESA are required to achieve target Hb levels.[281-284]

**Table 38. Published Experience in Patients With Anemia, CKD, and a Preexisting Hematologic Disorder**

| Author, Year | Location | Adult/Ped/ Mean Age | N | Diagnosis | Type of Study | EPO | Response |
|---|---|---|---|---|---|---|---|
| Cheng, 1993 [281] | China | Adult | 4 | Thal-t | (n = 4 ) Matched controls | Different doses | Higher doses of ESA to achieve target Hb |
| | | | 1 | HbH | | | Resistant to ESA |
| Lai, 1992 [283] | China | Adult | 4 | α-Thal-T, β-Thal-m | (n = 36) Randomly selected | Different doses | Poor response of Thal patients |
| Di Iorio, 2003 [282] | Italy | Adult | 10 | β-Thal-m | Lab quantification of Hb chains | Different doses | ESA dose requirement higher in patients with high levels of anomalous Hb chains |
| Powe, 1993 [288] | US | Adult | 59,462 | CKD Stage 5 | National logitudinal cohort | Epo requirement | |
| | | | | Multiple myeloma | | | Less response, higher ESA requirement |
| | | | | Sickle cell disease | | | Less response, higher ESA requirement |
| Tomson, 1992 [289] | UK | Adult | 3 | Sickle cell disease | Case reports | Increasing doses | No sickle crisis on ESA, Hb S increased, no Tf for 12 weeks |
| Tarng, 1997 [296] | Taiwan | Adult | 1 | Hb J-Meinung | Case reports | | Poor response to ESA |
| Drueke, 1990 [297] | France | | | | Review | | |
| Ataga, 2000 [298] | US | | | | Review | | |
| Drueke, 1991 [299] | France | | | | Review | | |
| Di Iorio, 2004 [284] | Italy | | 12 | β-Thal-m | Case series | Increasing doses | Patients became Tf independent on high doses of ESA, sustained effect |
| Di Iorio, 2003 [282] | Italy | | 10 | β-Thal-m | Case series | HbA2 levels and Epo | Need for ESA increases with presence of high levels of Hb $A_2$ chains (see Ataga, 2000 [298]) |
| Paritpokee, 2002 [285] | Thailand | Children | 5 | β-Thal-t | Lab for endogenous Epo | Lab study | β-Thal major high levels of ESA |
| | | | 15 | Hb E-t | | | |
| | | | 55 | β-Thal-m/Hb E | | | |
| Papassotiriou, 2000 [290] | Greece | | 3 | Homocyg sickle cell disease | Intervention with HU | Endogenous Epo levels | ESA levels increase on HU |
| | | | 10 | Hb S/β-Thal | | | |
| Papassotiriou, 1998 [287] | Greece | | 20 | Hb H | Case series | Epo and TfR levels | Both are increased in patients with HbH/ineffective erythropoiesis/hemolysis |
| Katopodis, 1997 [286] | Greece | 16-59 | 17 | S-β-Thal | Comparison with normal controls | Epo levels, Hb | High ESA levels in S-β-Thal compared to normal, correlation with Hb |

- Patients can become independent of transfusions on high doses of ESA.[284]
- The need for ESA increases in patients with high levels of $Hb_{A2}$ chains in the serum.[282]
- Patients with $\beta$-thalassemia major show high endogenous erythropoietin levels.[285]
- Patients with HbS/$\beta$-thalassemia have a higher-than-normal endogenous erythropoietin level.[286]

*Hb H*

- Patients are resistant to ESA.[281,287]
- Endogenous serum erythropoietin levels and serum transferrin receptor levels are both increased.[287]
- The mechanism of anemia is likely related to ineffective erythropoiesis and hemolysis.[287]

*Hb S*

- Patients show higher ESA dose requirement to achieve target Hb level.[288,289]
- There may be a lower incidence of sickle cell crises while on ESA therapy.[289]
- Endogenous erythropoietin levels increase with hydroxyurea therapy.[290]

*Multiple Myeloma*

- Higher levels of ESA are required to achieve target Hb levels in patients with HD-CKD.[288]
- Therapy with ESAs reduces transfusions and improves QOL in anemic patients with or without kidney disease.[291]

### *General Comments*

Patients with $\beta$-thalassemia and Hb S disease may require higher doses of ESA compared with patients with CKD who do not have hematologic disorders. There is no apparent contraindication to increase the ESA dose in either disorder. Some patients may require doses usually used in hematopoietic disorders (40,000 to 60,000 U/wk).

### *Evaluation for PRCA*

*Evaluation for antibody-mediated PRCA should be undertaken when a patient receiving ESA therapy for more than 4 weeks develops each of the following: sudden rapid decline in Hb level at the rate of 0.5 to 1.0 g/dL/wk, or requirement of red blood cell transfusions at the rate of approximately 1 to 2 per week; normal platelet and white blood cell counts; and absolute reticulocyte count less than 10,000/$\mu$L.*

*Syndrome Recognition*

The characteristic sign of PRCA is almost complete cessation of erythropoiesis. Accordingly, a patient affected with PRCA evidences a decrease in Hb level of about 0.1 g/dL per day and a reticulocyte count less than 10,000/$\mu$L, consistent with the normal rate of red blood cell destruction and an absence of red blood cell production. Because nonerythroid marrow is unaffected, leukocyte and platelet counts are expected to be normal.[274,276]

*Diagnostic Evaluation*

Recommendations based on expert opinions have been published to guide the workup and therapy of patients suspected to have antibody-mediated PRCA.[274,277,279] The definitive diagnosis is dependent upon demonstration of the presence of neutralizing antibodies against erythropoietin.

*Management and Treatment*

It is prudent to discontinue the administration of any ESA product in patients with suspected and confirmed diagnosis because the antibodies are cross-reactive and continued exposure may lead to anaphylactic reactions.[292] Patients likely will require transfusion support. Treatment with immunosuppressive approaches is effective in a significant number of patients.[293] Renal allografts usually result in a rapid decrease in antibody titers associated with therapeutic benefit.[293] It is not clear whether treatment with ESA can be resumed safely after clearance of the antibody. Based on very preliminary data, this might be feasible; however, caution is advised.[294] A single case also has been reported in which Hb levels could be restored in the presence of antierythropoietin antibodies by switching to a different product.[295]

# III. CLINICAL PRACTICE RECOMMENDATIONS FOR ANEMIA IN CHRONIC KIDNEY DISEASE IN CHILDREN

## CLINICAL PRACTICE RECOMMENDATIONS FOR ANEMIA IN PEDIATRIC PATIENTS WITH CKD

### INTRODUCTION

Presentation of clinical practice recommendations for anemia in pediatric patients with CKD is warranted because the pediatric patient population, from newborn through adolescence, differs substantially from the adult population in key metabolic, growth, developmental, and psychological factors.[300] Nevertheless, providers caring for adult and pediatric patients with CKD largely share the same topics of concern regarding the diagnosis and management of anemia. Moreover, the bulk of information to support CPRs and the only evidence of sufficient strength to support evidence-based guidelines are available from studies of the adult patient population. Given the distinct needs of pediatric patients, shared topics of concern among providers for both pediatric and adult patients, the generally low quality of evidence in pediatric patients, and the unavoidable need to generalize from evidence in adults, the Work Group chose to present CPRs in pediatric patients as a separate section, using adult guidelines as a frame of reference, changing recommendations when appropriate, and describing available evidence in pediatric patients under the guideline rationale.

Here, we address issues pertinent to children with anemia and CKD at all stages of disease. Our goal is to offer recommendations based on the best evidence available regarding issues related to the identification, diagnosis, initial evaluation, and strategies for treatment and monitoring of children with anemia and CKD stages 1 to 5, including those treated with dialysis. Our review is not exhaustive and our intent is not to substitute for textbooks. Specific details on potential dosing regimens, therapeutic choices, and practice options in caring for children with anemia and CKD are found elsewhere.[301]

Please note that to be consistent with the use of Hb levels, as opposed to Hct, in these new guidelines, all Hct values from studies quoted have been converted to Hb equivalents by a factor of 0.3 g/dL per percent of Hct; eg, an Hct of 33% is converted to an Hb level of 9.9 g/dL.

All statements in the pediatric section assume the preface *In the opinion of the Work Group,* and all statements are provided as CPRs because there is insufficient evidence in pediatric patients to support evidence-based guidelines. When, in the opinion of the Work Group, the adult guideline statement applies equally well to adults and children, the statement is accompanied by the following:

***(FULLY APPLICABLE TO CHILDREN)***

When, in the opinion of the Work Group, the adult guideline statement needs modification or adjustment for children, the following instruction is given, followed by the pediatric-specific guideline statement.

***(APPLICABLE TO CHILDREN, BUT NEEDS MODIFICATION)***

# CPR FOR PEDIATRICS 1.1: IDENTIFYING PATIENTS AND INITIATING EVALUATION

Identifying anemia is the first step in evaluating the prognostic, diagnostic, and therapeutic significance of anemia in patients with CKD.

**1.1.1 Stage and cause of CKD:** ***(FULLY APPLICABLE TO CHILDREN)***

**In the opinion of the Work Group, Hb testing should be carried out in all patients with CKD, regardless of stage or cause.**

**1.1.2 Frequency of testing for anemia:** ***(FULLY APPLICABLE TO CHILDREN)***

**In the opinion of the Work Group, Hb levels should be measured at least annually.**

**1.1.3 Diagnosis of anemia:** ***(APPLICABLE TO CHILDREN, BUT NEEDS MODIFICATION)***

**ADULT CPR**

**In the opinion of the Work Group, diagnosis of anemia should be made and further evaluation should be undertaken at the following Hb concentrations:**

- **<13.5 g/dL in adult males.**
- **<12.0 g/dL in adult females.**

**PEDIATRIC CPR**

***In the opinion of the Work Group, in the pediatric patient, diagnosis of anemia should be made and further evaluation should be undertaken whenever the observed Hb concentration is less than the fifth percentile of normal when adjusted for age and sex.***

## RATIONALE

### *Stage and Cause of CKD*

There is no evidence in the pediatric CKD population to contradict the principles as outlined in the Adult Guideline 1.1 with respect to the use of Hb level, not Hct, to define anemia and the value of obtaining this at a standard time (eg, before dialysis during the midweek run) in patients on HD therapy.

It also is clear that children with CKD are more likely to develop anemia as their renal function decreases. From USRDS 2004 data, we know that the mean eGFR at initiation of dialysis therapy in children is 10.3 mL/min/1.73 $m^2$ and that, at this point, 35% to 40% of children are already receiving ESA therapy.[28] One study of 35 children with various degrees of renal disease examined the role of erythropoietin and potential inhibitors of its action. The study suggested that in this group, the risk for anemia increased at a GFR less than 35 mL/min/1.73 $m^2$.[302] Unfortunately, unlike the adult literature, there is no better direct or observational evidence that clearly delineates a particular cutoff level of function for which the risk for CKD-associated anemia increases significantly in children.

### *Frequency of Testing for Anemia*

This guideline is considered applicable to children because there is no direct evidence to support a different recommendation. However, it is often the case that children (especially younger ones) will receive more frequent laboratory monitoring of their CKD status caused, in part, by expected changes in values during growth.

### *Diagnosis of Anemia*

In terms of defining a lower limit of "normal" Hb level before initiating a workup for anemia in a child with CKD, it seems reasonable to apply the same approach, although not the same values, as in the adult Guidelines. In other words, anemia in a child with CKD should be diagnosed and evaluated at such time that the child's Hb level decreases to less than the fifth percentile for their age and sex. Adjustment in normal Hb levels—and hence the definition of anemia—for children living at higher altitudes likely is reasonable, as in the adult Guidelines, although age-specific pediatric data are not available.

The normative values for this definition in children older than 1 year of age have been taken from the NHANES III reference data, as in adults (Table 39), whereas the values for children from birth to 1 year are taken from data compiled elsewhere (Table 40).[303]

**Table 39. Hb Levels (g/dL) in Children Between 1 and 19 Years for Initiation of Anemia Workup[a]**

| All Races/Ethnic Groups | Number of Subjects | Mean | Standard Deviation | Anemia Definition Met if Value is <5th Percentile |
|---|---|---|---|---|
| *BOYS* | | | | |
| 1 yr and over | 12,623 | 14.7 | 1.4 | 12.1 |
| 1-2 yr | 931 | 12.0 | 0.8 | 10.7 |
| 3-5 yr | 1,281 | 12.4 | 0.8 | 11.2 |
| 6-8 yr | 709 | 12.9 | 0.8 | 11.5 |
| 9-11 yr | 773 | 13.3 | 0.8 | 12.0 |
| 12-14 yr | 540 | 14.1 | 1.1 | 12.4 |
| 15-19 yr | 836 | 15.1 | 1.0 | 13.5 |
| *GIRLS* | | | | |
| 1 yr and over | 13,749 | 13.2 | 1.1 | 11.4 |
| 1-2 yr | 858 | 12.0 | 0.8 | 10.8 |
| 3-5 yr | 1,337 | 12.4 | 0.8 | 11.1 |
| 6-8 yr | 675 | 12.8 | 0.8 | 11.5 |
| 9-11 yr | 734 | 13.1 | 0.8 | 11.9 |
| 12-14 yr[b] | 621 | 13.3 | 1.0 | 11.7 |
| 15-19 yr[b] | 950 | 13.2 | 1.0 | 11.5 |

a. Based on NHANES III data, United States, 1988-94; data abstracted from Tables 2 & 3.[40]
b. Menstrual loses contribute to lower mean and 5th percentile Hb values for group.



**Table 40. Hb Levels (g/dL) in Children Between Birth and 24 Months for Initiation of Anemia Workup [a]**

| Age | Mean Hb | –2 SD[b] |
|---|---|---|
| Term (cord blood) | 16.5 | 13.5 |
| 1-3 d | 18.5 | 14.5 |
| 1 wk | 17.5 | 13.5 |
| 2 wk | 16.5 | 12.5 |
| 1 mo | 14.0 | 10.0 |
| 2 mo | 11.5 | 9.0 |
| 3-6 mo | 11.5 | 9.5 |
| 6-24 mo | 12.0 | 10.5 |

a. Data taken from normal reference values.[303]
b. Values 2 standard deviations below the mean are equivalent to <2.5th percentile

# CPR FOR PEDIATRICS 1.2: EVALUATION OF ANEMIA IN CKD

Anemia in patients with CKD is not always caused by erythropoietin deficiency alone. Initial laboratory evaluation therefore is aimed at identifying other factors that may cause or contribute to anemia or lead to ESA hyporesponsiveness.

**1.2.1 In the opinion of the Work Group, initial assessment of anemia should include the following tests: *(APPLICABLE TO CHILDREN, BUT NEEDS MODIFICATION)***

**1.2.1.1 A CBC including—in addition to the Hb concentration—red blood cell indices (MCH, MCV, MCHC), white blood cell count and differential and platelet count.**

**1.2.1.2 Absolute reticulocyte count.**

**1.2.1.3 Serum ferritin to assess iron stores.**

**1.2.1.4 <u>ADULT CPR</u>**
**Serum TSAT *or* CHr to assess adequacy of iron for erythropoiesis.**
**<u>PEDIATRIC CPR</u>**
***In the pediatric patient, serum TSAT to assess adequacy of iron for erythropoiesis.***

**RATIONALE**

There is no evidence to support any different recommendations in children compared with adults with respect to statements 1.2.1.1 through 1.2.1.3. However, tests other than TSAT that are included in the recommendation for assessment of iron available for erythropoiesis in adults have not been well studied in the pediatric CKD population, with only 2 studies examining the use of CHr in HD patients[304,305] and none evaluating the use of PHRCs. This would seem to suggest that until further data are available, these tests remain research-based methods in children with CKD.

# CPR FOR PEDIATRICS 2.1: HB RANGE

Treatment thresholds in anemia management describe the intended goal of current treatment for the individual patient. The Hb treatment range represents the intended goal of ESA and iron therapy.

**2.1.1 Lower limit of Hb:** ***(FULLY APPLICABLE TO CHILDREN)***
**In patients with CKD, Hb level should be 11.0 g/dL or greater.** ***(MODERATELY STRONG RECOMMENDATION)***

**2.1.2 Upper limit of Hb:** ***(FULLY APPLICABLE TO CHILDREN)***
**In the opinion of the Work Group, there is insufficient evidence to recommend routinely maintaining Hb levels at 13.0 g/dL or greater in ESA-treated patients.**

## RATIONALE

Determination of Hb targets in pediatric patients resists definitive recommendation. QOL, so significant to the development of the child and life of the family, lends urgency to the consideration of higher Hb level thresholds. However, evidence lacks both quality and quantity, rendering assessment of both benefit and risk uncertain. Age-specific variation in normal Hb levels introduces further uncertainty. Finally, given key metabolic, growth, developmental, and psychological differences between children and adults, exclusive reliance on evidence in adults is inappropriate.

The Work Group presents lower and upper targets for Hb levels in children using values in adults for reference. However, we add 2 significant qualifications. The first is that both the lower and upper Hb targets serve only as opinion-based CPRs, in keeping with the lack of pediatric-specific evidence. The second is that medical decision making to set Hb targets in individual patients should be informed by available evidence that is uniquely pediatric. Consideration should be given, for example, to the potential need to make adjustments for the normal age-specific Hb distribution (Table 39 and Table 40). In weighing the potential QOL benefits of Hb targets, the available evidence in adults should be enriched by consideration of QOL issues that are crucial to children, including neurocognitive development, school attendance, exercise capacity, and family support. To assist medical decision making, the Work Group provides the following review of the literature.

### *Mortality*

Observational evidence relating Hb level to mortality is available. Children in the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) database from 1992 to 2001 with an Hb level less than 9.9 g/dL compared with those with an Hb level greater than 9.9 g/dL showed an elevated risk for mortality: adjusted RR, 1.52; 95% CI, 1.03 to 2.26; $P < 0.05$.[306] The relationship between Hb level and mortality, when examined at other cutoff values for Hb, appeared continuous. Patients with more severe anemia also experienced increased risk for hospitalization (17.2% ± 1.8% versus 12.3% ± 2.1%, respectively; $P < 0.01$).

### *The Heart*

A single RCT provides evidence for the benefit of treatment of anemia with ESA compared with placebo. In a blinded crossover trial of 11 children aged between 2.3 and 12.3 years, undergoing HD or PD, and with a baseline Hb level between 4.3 and 8.1 g/dL, patients were assigned to either ESA therapy (Hb > 10 g/dL) or placebo for 24 weeks.[126] Seven patients completed both trial arms. ESA therapy was associated with partial correction of an elevated cardiac index by 6 months and a significant reduction in left ventricular mass by 12 months.

Two observational studies have examined the relationship between anemia and LVH in children with CKD.[307,308] In these studies, patients with severe LVH (left ventricular mass index > 51 g/m$^2$) showed a statistically lower Hb level than those without LVH (Hb, 9.5 ± 1.8 versus 10.9 ± 2.3 g/dL; $P = 0.027$). Left ventricular compliance also was related to Hb level in children ($r = –0.65$; $P = 0.02$). The findings suggest that severe anemia in children with CKD stage 5 leads to chronic increases in cardiac workload and a consequent increase in both left ventricular end-diastolic volume and mass.

In this RCT, exercise capacity improved with ESA treatment (mean achieved Hb, 11.2 g/dL; range, 9.5 to 14.2 g/dL) compared with placebo

control.[126] Measures of capacity significantly affected included a 2-minute walking test (n = 7) and a formal treadmill testing using the Bruce protocol, full (n = 3) or modified (n = 3). Distance walked, in meters, approached but did not reach statistical significance in the ESA arm of the crossover, $P = 0.06$; similar results were seen from both the regular or modified treadmill data, $P = 0.07$.

In a nonrandomized interventional trial, 18 children with CKD stage 5 (15 patients, on HD or PD) and a Hb level less than 9.9 g/dL were administered IV or SC ESA until Hb level was greater than 9.9 g/dL; baseline Hb level of 6.5 ± 0.8 g/dL changed to a final level of 10.0 ± 0.6 g/dL; $P = 0.001$.[309] Exercise time (treadmill with a modified Bruce protocol) increased significantly (before ESA, 10.3 ± 1.9 minutes; after ESA, 11.2 ± 1.9 minutes; $P = 0.01$), and resting oxygen consumption decreased from 7.8 ± 1.8 to 6.9 ± 1.4 mL/min/kg; $P = 0.01$ with the higher Hb level. However, there was no change in stroke volume, blood pressure, or any cardiac indices after the first month at the higher Hb level.

Similarly, a small cohort (n = 7) of HD patients showed an improvement in aerobic work capacity and effort tolerance, as evidenced by statistically significant changes in the workload reached, peak oxygen uptake, and average ventilatory anaerobic threshold after treatment of anemia with ESA (baseline Hb, 6.3 ± 0.9 g/dL versus final Hb, 11.2 ± 1.2 g/dL).[310]

Finally, 10 children undergoing PD were evaluated before and 18 months after limited correction of anemia with ESA (baseline Hb, 5.9 ± 0.9 g/dL versus final Hb, 8.7 ± 1.5 g/dL). Patients showed a significant slowing of heart rate, $P < 0.01$, but no improvement for other cardiac parameters.[311]

### *QOL and Neurocognitive Effects*

The relationship between QOL and anemia has been examined in children with CKD.[126,312,313] In 2 trials,[312,313] QOL instruments were not validated in patients with CKD and were completed by parents. Only 1 study blinded parent-responders to use of ESA or placebo, although 5 of 7 parents in that study correctly identified use of ESA during the appropriate treatment.[126]

In 116 children enrolled in a multicenter trial, sleep, activity (in school, at home, or in social situations), alertness, feelings, and a summary score composed of all subscores were assessed at baseline and every 6 months during ESA treatment to attain a target Hb level of 9.6 to 11.2 g/dL compared with baseline pretreatment Hb level of 6.7 g/dL (range, 3.4 to 9.5 g/dL).[313] Scores at 1 year after ESA increased after treatment for all aspects examined, but only the 10% increase in the summary score achieved significance ($P < 0.05$).

In the previously described randomized crossover trial,[126] a 25-question modified parental questionnaire used a visual analog scale to assess 5 domains: sleep, school performance, diet, psychosocial, and a physical performance/health construct. Only physical performance and general health showed a significant treatment effect (again, baseline Hb, 4.3 to 8.1 g/dL versus final Hb, 11.2 g/dL; range, 9.5 to 14.2 g/dL).

A generic health QOL questionnaire has been administered in a cross-sectional fashion to the parents of children with CKD stages 1 to 5 and transplant recipients.[312] This instrument, which has shown internal consistency and concurrent validity and has been used in a single-center trial of children on HD therapy,[314] measures 12 aspects of health-related QOL in the domains of physical functioning; limitations in schoolwork and activities with friends, general health, bodily pain and discomfort, limitations in family activities; emotional/time impact on the parent; impact of emotional or behavior problems on school work and other daily activities; self-esteem; mental health; behavior; family cohesion; and change in health. When evaluated as a continuous variable, Hct was linked directly to measures of improved health, as seen in the single-item general health ($r = 0.36$; $P = 0.003$), general health ($r = 0.29$; $P = 0.004$), and physical functioning ($r = 0.35$; $P = 0.0004$) domains.[312]

Further analysis of the same data, adjusting for eGFR, age, sex, race, dialysis modality, and transplantation or chronic renal insufficiency and dividing the patients into groups with Hb level greater than or less than 10.8 g/dL (defined by the investigators as anemic), showed an association between anemia and 4 domains: Parental Impact-Time, Family Activities, Role–Physical, and Physical Functioning. Further multivariate

analysis done after division of the group into Hb tertiles, less than 9.9 g/dL, 9.9 to 10.8 g/dL, and greater than 10.8 g/dL, showed a strong dose-response relationship between Hb level and health-related QOL as measured by this instrument. It should be noted that differences between the mid and upper tertile of Hb levels did not reach significance, whereas those between the lowest and upper tertile in the areas of Physical Functioning ($P = 0.02$), Role–Emotional ($P = 0.05$), Role–Physical ($P = 0.02$), Parental Impact–Time ($P = 0.004$), Family Activities ($P = 0.003$), and Physical Summary score ($P = 0.01$) did. (*Note:* these results have been converted from Hct to Hb values.)

The neurocognitive effects of anemia also have been examined. In healthy children aged 6 to 11 years, impairment in cognition is associated with iron deficiency and an Hb level less than 11.8 g/dL.[315] Furthermore, in a multicenter single-arm interventional trial evaluating 22 children with CKD aged 4 months through 16 years, treatment of anemia was associated with a significant increase in IQ, determined by using the Weschler intelligence test, although the relative increase in Hb levels was small (Hb baseline, 9.2 ± 1.6 versus final, 9.7 ± 1.7 g/dL; $P = 0.007$).[316]

### *Nutrition and Growth*

No reliable studies have been published that examine the relationship between treatment of anemia and nutrition in children. The literature consists largely of subjective reports by the child or family or short small trials that fail to achieve significant treatment effects.

Treatment of anemia apparently fails to reverse growth retardation in children with CKD undergoing HD or PD.[317,318] In a US phase III, randomized, double-blinded, placebo-controlled trial of ESA therapy in children, 81 children on HD or PD therapy showed a substantial increase in Hb levels with treatment (baseline, 6.3 to 6.6 g/dL to final, 9.3 g/dL), and no effect was seen for any measured nutrition or growth parameter, including midarm circumference, triceps skinfold thickness, weight gain, or the SD scores for growth velocity or height.[317]

### *Hypertension*

The development or worsening of hypertension during treatment with ESAs in children is of significant concern. In a study of children aged 4 months to 21 years, assignment to either high-dose (epoetin, 450 IU/kg/wk) or low-dose (150 IU/kg/wk) ESA treatment was associated with a significant increase in diastolic blood pressure by week 12 compared with baseline (88 ± 6.7 versus 68 ± 17 mm Hg; paired *t*-test, $P = 0.01$).[319] The investigators reported a nonsignificant trend between increasing Hb levels and increasing systolic and diastolic blood pressures despite stable or lower ESA dose.

### *Thrombotic Events*

No thrombotic events, including vascular access thrombosis, were reported in either arm of the mentioned high-dose versus low-dose ESA trial.[319] However, the small number of patients, relatively short length of follow-up, and relatively few patients with HD preclude any reliable conclusions about safety. No other larger prospective trials of pediatric patients treated with ESAs to various Hb targets are available to further address the issue of clotting or access thrombosis, although it has been reported to occur intermittently in children.[318,320–323]

### *ESA Therapy and Loss of Renal Function*

In patients with ND-CKD assigned to high-dose compared with low-dose ESA treatment, no significant difference in creatinine levels was seen; in the same trial, between-group comparison showed no change in Kt/V among patients with HD-CKD.[319]

# CPR FOR PEDIATRICS 3.1: USING ESAs

ESAs are critical components in managing the anemia of patients with CKD. Available ESAs are each effective in achieving and maintaining target Hb levels. Aspects of administration may differ between short-acting and long-acting agents.

**3.1.1 Frequency of Hb monitoring: *(FULLY APPLICABLE TO CHILDREN)***

**3.1.1.1 In the opinion of the Work Group, the frequency of Hb monitoring in patients treated with ESAs should be at least monthly.**

**3.1.2 ESA dosing: *(FULLY APPLICABLE TO CHILDREN)***

**3.1.2.1 In the opinion of the Work Group, the initial ESA dose and ESA dose adjustments should be determined by the patient's Hb level, the target Hb level, the observed rate of increase in the Hb level, and clinical circumstances.**

**3.1.2.2 In the opinion of the Work Group, ESA doses should be decreased, but not necessarily held, when a downward adjustment of Hb level is needed.**

**3.1.2.3 In the opinion of the Work Group, scheduled ESA doses that have been missed should be replaced at the earliest possible opportunity.**

**3.1.2.4 In the opinion of the Work Group, ESA administration in ESA-dependent patients should continue during hospitalization.**

**3.1.2.5 In the opinion of the Work Group, hypertension, vascular access occlusion, inadequate dialysis, history of seizures, or compromised nutritional status are not contraindications to ESA therapy.**

**3.1.3 Route of administration: *(APPLICABLE TO CHILDREN, BUT NEEDS MODIFICATION)***

**3.1.3.1 <u>ADULT CPR</u>**

**In the opinion of the Work Group, the route of administration should be determined by the CKD stage, treatment setting, efficacy considerations, and the class of ESA used.**

**<u>PEDIATRIC CPR</u>**

***In the opinion of the Work Group, in the pediatric patient, the route of administration should be determined by the CKD stage, treatment setting, efficacy considerations, the class of ESA used, and the anticipated frequency and pain of administration.***

**3.1.3.2 In the opinion of the Work Group, convenience favors SC administration in non–HD-CKD patients.**

**3.1.3.3 In the opinion of the Work Group, convenience favors IV administration in patients with HD-CKD.**

**3.1.4 Frequency of administration: (*APPLICABLE TO CHILDREN, BUT NEEDS MODIFICATION*)**

**3.1.4.1 <u>ADULT CPR</u>**

**In the opinion of the Work Group, frequency of administration should be determined by the CKD stage, treatment setting, efficacy considerations, and class of ESA.**

**<u>PEDIATRIC CPR</u>**

***In the opinion of the Work Group, in the pediatric patient, the frequency of administration should be determined by the CKD stage, treatment setting, efficacy considerations, and class of ESA; as well, consideration should be given to the anticipated frequency of, and pain on administration of each agent and their potential effects on the child and family.***

**3.1.4.2 In the opinion of the Work Group, convenience favors less frequent administration, particularly in non–HD-CKD patients.**

**RATIONALE**

***Frequency of Hb Monitoring***

This guideline is considered applicable to children because there are some data supporting this assumption and there is no reason for a different recommendation.

There are 2 reasons that may justify closer monitoring of all pediatric patients with 1- to 2-week Hb levels when *initiating and/or making significant change to the ESA dose*. The first is to ensure that the patient is responding to the current dose. Although not as well described in children as in adult literature, it likely is true that a patient who will reach an intended 1-g/dL increase in Hb level after 1 month of a given ESA/iron regimen will have that increase occur relatively evenly over each of the 4 weeks. In other words, blood work weekly or every 2 weeks will allow the clinician to institute an increase in dosing if a rate of increase of approximately 0.25 g/dL per week is not seen in the early part of the month. (In adults, the rate of increase has been estimated to be 0.3 g/dL per week [0.2 to 0.5 g/dL] on appropriate doses of rHuEPO.[324])

Similarly, a child for whom the rate of increase appears rapid, eg, greater than 0.5 g/dL per week, could have the dose adjusted before overshooting at the end of that month of therapy. The greater frequency of monitoring likely is beneficial until the patient has reached a target Hb level and is on a stable dose of ESA. At this point, less frequent monitoring may be indicated, eg, every 4 weeks.

***ESA Dosing***

In the opinion of the Work Group, this guideline is applicable in children, but needs some modification or adjustment.

***Initial Dose and Dose Adjustments***

Although there are many dosing guidelines for the use of ESAs in children, it is important to realize that, as in adults,[123] there is a large variation in pediatric dosing of these drugs.[325] Currently, the most robust evidence for dosing ESA products in children is related to erythropoietin alfa and beta products, with information on darbepoietin alfa dosing just now becoming available.

All clinicians are advised to carefully evaluate the individual patient's particular issues related to their Hb level and likely response before deciding on a particular ESA product, dosing regimen, and frequency of monitoring before the initiation of or changes in ESA and/or iron therapies.

The following section is divided into dialysis versus nondialysis patients and short-acting versus long-acting ESA products.

***Dialysis Population (HD and PD)***

1. *Short-acting ESAs.* Data from the latest NAPRTCS annual report highlight the variation in initial dose reported in children on dialysis therapy, with the younger child consistently receiving more rHuEPO on a per-kilogram-per-week basis.[325] The doses referred to next are not derived from RCTs, but rather from registry data and therefore should be interpreted with caution. They represent approximations of the dose required in an average cohort of children and are not represented as recommendations for any specific child. (Note that 93% of these patients were administered erythropoietin alfa as Epogen®; Amgen, Thousand Oaks, CA.)

This variation in dosing can be seen in relation to:

a) *The dialysis modality*, with PD patients initially requiring approximately 225 U/kg/wk compared with nearly 300 U/kg/wk of erythropoietin alfa products to achieve target Hb levels for those on HD therapy.[325] Interestingly, this difference in dosing disappears during the first 18 to 30 months of follow-up. It should be noted that the initial dosing difference persisted even when both groups of patients were administered the ESA SC[326] and may be caused in part by such factors as blood loss and the use of IV ESAs in HD patients as opposed to SC ESAs in PD or nondialysis patients.[319]

b) *Age*, with patients younger than 1 year requiring an average of 350 U/kg/wk; those 2 to 5 years, approximately 275 U/kg/wk; those 6 to 12 years, 250 U/kg/wk; and finally those older than 12 years needing only slightly more than

200 U/kg/wk at the time of starting ESA therapy.[325] One report speculates that this apparently increased "clearance" of erythropoietin in a young child is caused by the presence of nonhematopoietic binding sites for the erythropoietin molecule,[327] which—in the fetus or developing child—appears to function as a nonhematopoietic cellular growth factor.[328] Because internalization and, potentially, degradation of some of the erythropoietin dose would limit the amount of hormone available for stimulating erythropoiesis, one could explain the need for higher absolute doses to achieve a given marrow response or Hb production. Furthermore, the authors speculate that as the child ages, the number of these sites decreases as development slows, with an attendant decrease in the absolute hematopoietic dose of erythropoietin required.[327]

No major differences were noted in relation to either race or sex with respect to initial ESA dose required. There was a general tendency for all doses to decrease over time, presumably on the basis of a lower amount of ESA being required to maintain—as opposed to reach—a given Hb target.

2. *Long-acting ESAs.* Currently, there are only 3 published articles[329-331] and 1 abstract[332] in the peer-reviewed literature related to long-acting ESA products and children with CKD, including those on dialysis therapy. It is expected that there will be other results in due course to assist in guiding the pediatric practitioner in using longer acting ESA agents more effectively.

The first study evaluated the pharmacokinetic properties of darbepoetin alfa in children with CKD and compared the results with prior studies published in adults.[330] They showed that clearance, drug half-life, and bioavailability of darbepoetin alfa, whether administered IV or SC, were similar between pediatric and adult patients. The 1 difference was that absorption of the drug administered SC appeared to be more rapid in pediatric than adult patients.

The second study described the clinical use of darbepoietin alfa in children.[329] The investigators switched 7 long-term HD patients aged 11.5 years (range, 7 to 15.2 years) with a stable Hb level on erythropoietin therapy to darbepoietin IV therapy. Results from this small study suggest that (at least in the pediatric HD population) the conversion dose of erythropoietin alfa to darbepoietin is more likely to be closer to 0.5 $\mu$g for every 200 U of erythropoietin alfa, rather than the 1 $\mu$g/200 U conversion recommended by the manufacturer. The authors themselves suggest a wide range of doses, 0.25 to 0.75 $\mu$g/kg/wk, as being reasonable for the initial switch between therapies.

The most recent report prospectively looked at the use of darbepoetin alfa in 8 children on PD therapy, 6 children on HD therapy, and 12 children with ND-CKD.[331] All patients weighed more than 8 kg and were younger than 18 years. Therapy with ESAs was initiated, if the patient was ESA-naïve, when Hb level was less than 10.0 g/dL, and only patients judged iron-replete, TSAT greater than 20%, were included. The primary outcomes were: (1) the proportion of patients with a mean Hb level greater than 10.0 g/dL between weeks 8 and 12 and then weeks 20 to 28 of the study, and (2) the percentage of all Hb values greater than 10.0 g/dL at each time point.

The initial dose of darbepoetin alfa was 0.45 $\mu$g/kg/wk, administered IV in the HD patients and SC in the PD and ND-CKD patients. Much of the data are presented in aggregate and include both the 26 patients enrolled prospectively and 7 more patients enrolled retrospectively. Statistical analysis by the investigators did not show a difference in terms of drug dose between the beginning and end of the study ($P = 0.77$), and there was no difference in doses between the HD, PD, and ND-CKD groups ($P = 0.62$) regardless of their being in the prospective or retrospective arm of the study ($P = 0.92$ and $P = 0.73$, respectively).

Data from 23 patients in the prospective cohort, 18 of whom were available at weeks 20-28 for analysis, showed a statistically significant increase in Hb levels at 8 to 12 weeks of 11.7 $\pm$ 1.1 g/dL compared with the baseline of 10.5 $\pm$ 1.0 g/dL ($P = 0.002$), which was still present at week 20 to 28 when Hb level was now 11.4 $\pm$ 0.9 g/dL ($P = 0.01$ compared with baseline). In this group, 96% (CI, 0.90 to 1.0; $P = 0.03$) compared with baseline at 8 to 12 weeks and 94% (CI, 0.72 to 0.99; $P = 0.06$) compared with baseline at 20 to 28 weeks had mean Hb values greater than 10.0 g/dL. Similarly, proportions of patients with total Hb values greater than 10.0

g/dL were 94% at 8 to 12 weeks and 90% at 20 to 28 weeks.

In all ESA-naïve patients (n = 8), the average time to reach the target of 10.0 g/dL from baseline of 9.0 ± 1.4 g/dL was 3.4 weeks, with no patient requiring a higher dose of darbepoetin alfa to achieve this.

The overall Hb response to darbepoetin alfa was related to the age of the patient, higher values for a given dose being achieved in older patients ($P = 0.02$).

Only 1 patient experienced a serious AE that was thought to be possibly related to the darbepoetin alfa. In this case, a girl on home HD therapy was admitted with a worsening of her hypertension; this was at a time when her Hb level was 13.2 g/dL but concurrent with a withdrawal from clonidine some 18 days before the admission. Her blood pressure subsequently was well controlled on fewer medications while remaining on darbepoetin alfa therapy.

### *Nondialysis Population*

1. *Short-acting ESAs.* In the ND-CKD population, a number of studies looked at the dose of rHuEPO required to achieve set targets. Currently, there is only 1 published prospective randomized trial that has looked at rHuEPO dosing in children with ND-CKD.[319] In this trial, 25 predialysis patients, CKD stages 3 to 5 but not on PD or HD therapy, were randomized to either 150 U/kg/wk (n = 12) or 450 U/kg/wk (n = 13) of rHuEPO administered SC in 3 divided doses. In all 12 of the 150-U/kg/wk patients and 11 of 13 of the 450-U/kg/wk patients, the Hb target of less than 2 SDs less than, but less than the mean for age, was achieved. When at target, the dose was reduced to maintain the target Hb level; on average, this required 143 ± 102 U/kg/wk for the group of responders.

A nonrandomized open-labeled prospective study took 11 patients aged 0.6 to 17 years with the equivalent of CKD stages 4 and 5 (all predialysis) whose mean Hb level was 7.9 g/dL and treated them with a single dose of 150 U/kg/wk of SC rHuEPO.[333] An increase in Hb level greater than 2 g/dL was seen in all 11 patients in a mean of 45 days, range of 14 to 119 days, and subsequently, the patients maintained Hb levels between 11.5 and 13.5 g/dL, with a mean dose of 133 U/kg/wk, range of 75 to 300 U/kg/wk.

A trial reported on behalf of the Australian and New Zealand Paediatric Nephrology Association also looked at the use of SC ESA in predialysis children.[316] Unfortunately, although 10 of the 22 patients were predialysis, their study does not allow the data to be abstracted specifically for this group.

2. *Long-acting ESAs.* As discussed in more detail in the preceding section (Long-Acting ESAs in the Dialysis Population), a study showed similar efficacy of darbepoetin alfa in the 15 patients, 12 prospectively enrolled, with ND-CKD treated with a dose of 0.45 $\mu$g/kg/wk.[331]

### *Rate of Increase in Hb Levels*

A few pediatric studies provide some information on which to base recommendations on the safety and side effects related to the rate of increase in Hb levels.

A prospective trial that examined the safety of rHuEPO therapy in children on HD or PD therapy or predialysis, randomized 44 children (aged 4 months to 21 years) to either low (150 U/kg/wk) or high (450 U/kg/wk) doses of epoetin alfa administered in 3 divided doses.[319] Patients were followed up for a total of 12 weeks and targeted for individual Hb levels of between 2 SD less than and the mean value for that child's age. Taking the groups as a whole, there was an average increase of 4.2 ± 2.1 versus 2.4 ± 1.5 g/dL per month in the high-dose versus low-dose groups. Hypertension appeared to be more common, but did not reach statistical significance, for those in the high-dose group compared with the low-dose group, 8 of 21 versus 5 of 23 patients, respectively; chi-squared $P = 0.17$. The investigators noted that the trend in systolic and diastolic blood pressure was to increase as Hb level increased. No other side effects seemed related to the rate of increase in Hb levels.

Another study randomized 20 anemic children 5 to 16 years of age who were on a stable continuous ambulatory PD regimen for 3 months to examine the effects of low-dose rHuEPO, 50 U/kg/wk (group A), versus high-dose rHuEPO, defined as 50 U/kg 3 times a week (group B).[334] Translating their data to Hb values from Hct, those in group A showed a steady increase over 6 months from an Hb level of approximately 6.3 g/dL to 9.9 g/dL compared with the increase seen in group B, for which Hb level went from 6.4 to

10.7 g/dL in only 3 months; an approximately 0.6-g/dL increase per month in group A versus 1.4-g/dL increase per month in group B. Although mean arterial blood pressure increased in both groups during the study (group A, 83 to 87 mm Hg; group B, 85 to 101 mm Hg), it only reached statistical significance in group B, $P < 0.05$. This was borne out by the need to increase the baseline antihypertensive medications in 8 of the 10 group B patients and initiate these medications in the remaining 2 patients in this group. (*Note*: rHuEPO therapy was discontinued briefly in 4 patients in group B; 2 patients because of hypertensive encephalopathy; conversely, no patient in group A required an increase in antihypertensive medication or initiation of such therapy during the study.)

If one examines a number of recent pediatric recommendations for the acceptable rate of increase in Hb values, they vary widely. One group recommends a rate of increase between 1 and 2 g/dL per month for all children below the target range.[301] Recent guidelines from the European Paediatric Peritoneal Dialysis Working Group recommend an increase of approximately 0.66 g/dL per month as minimally acceptable[335] and an increase of more than approximately 2.5 g/dL per month as unacceptable. An often-quoted study recommends, without evidence, that the goal should be an increase in Hb of 1 g/dL per month.[336]

*ESA dosing should be decreased, not held, if Hb level is elevated.* In the opinion of the Work Group, this guideline is fully applicable to children.

*Missed ESA doses.* In the opinion of the Work Group, this guideline is fully applicable to children. *ESA dosing during hospitalizations.* In the opinion of the Work Group, this guideline is fully applicable to children.

*Contraindications to ESA therapy.* In the opinion of the Work Group, this guideline is fully applicable to children.

### *Route of Administration*

As in adults, convenience in an outpatient setting favors use of the SC route for delivery of ESAs; with the added realization that even in the face of IV access, a short-acting ESA product will be more efficacious administered SC compared with IV, as confirmed in an observational trial in children.[325]

As of the 2004 NAPRTCS annual report, 96% of children on PD therapy were administered an ESA by the SC route as opposed to only 14% in the HD population.

However, in children, the psychological impact of frequent and/or painful injections also is important to assess when deciding on a dosing route. Currently, the single-dose preloaded syringes of both epoetin alfa (Eprex®) and darbepoietin alfa available in many parts of the world do not contain benzyl alcohol, which acts as a local anesthetic, in the epoetin alfa multidose vials. This means that injections with the preloaded Eprex® syringes generally are more painful than those from the multidose vials. Similarly, in a Canadian study, 8 of 14 patients with prior experience using epoetin alfa (Eprex®) reported that darbepoetin alfa caused more pain on injection; the remaining 6 patients did not specifically comment about whether they believed Eprex® caused more pain on injection.[331]

*Note*: Multidose vials of epoetin alfa *should be avoided if at all possible in premature infants and newborns* because of a rare, but well-recognized, complication from the use of benzyl alcohol in the preparation of the compound. This excipient has been described to cause numerous serious and potentially fatal reactions, including metabolic acidosis, intraventricular hemorrhage, and neurological problems. Sixteen neonatal deaths were reported that were thought to be caused by benzyl alcohol toxicity, generally described as the so-called "gasping syndrome."[337,338]

The issue of dosing epoetin alfa through the intraperitoneal route in children to eliminate injection pain also has been studied by various investigators.[339,340] In general, the added costs because of a higher dose required to achieve the same target Hb level, the need for at least 1 dry day dwell (or more) per week to achieve the epoetin alfa absorption required, and the potential for more frequent episodes of peritonitis have lead most centers away from use of this modality routinely. As of the 2004 NAPRTCS report, less than 2% of children on PD therapy currently are administered epoetin alfa through the peritoneal cavity.[325] At present, there are no data available on the use of darbepoietin alfa intraperitoneally.

### *Frequency of Administration*

As in the adult population, there is a move toward extending the dosing interval of all ESA products to minimize injections while maintaining efficacy of the product; ie, not having to increase dose significantly more than the gain in time between dosing, to maintain or achieve the target Hb level.

1. *Short-acting ESAs.* At present, there is no RCT evidence to show that this strategy is appropriate in children with the current short-acting ESA products on the market. However, data from the 2004 NAPRTCS annual report highlight that 75% to 80% of children on HD therapy will receive short-acting ESA products IV during a standard (3 times per week) HD regimen, whereas a smaller number (15% to 20%) receive it twice a week, and other dosing regimens are uncommon. However, 70% of children on PD therapy generally receive only once-weekly or perhaps twice-weekly injections, with 25% receiving injections thrice weekly, and approximately 5% receiving the drug less than once per week.[325]

It also may be reasonable on occasion to consider more frequent SC dosing of the short-acting ESAs, eg, thrice weekly, when the patient's Hb level is well less than the target Hb desired, although the absolute rate of increase should not exceed 2 g/dL per month. Here, the more-frequent dosing ensures that the therapeutic threshold of the hormone is maintained, given its short half-life, and—in concert with adequate iron stores—may assist in achieving a more rapid increase in Hb level.

2. *Long-acting ESAs.* Data on the dosing frequency of darbepoietin alfa in pediatric HD patients comes from 7 patients, all of whom were dosed once weekly after HD.[329] From a pharmacokinetic study,[330] it is clear that extended-dosing regimens with darbepoietin alfa in children should be possible, although currently, few data have been published outlining strategies for dosing frequency.

In 1 study, to appropriately dose patients at 0.45 $\mu$g/kg/wk with the available preloaded darbepoetin alfa syringes, the investigators started 63% of their patients on every 10-, 14-, or 21-day dosing regimens; the remainder were on once-weekly dosing.[331] Their results showed no impact of the various dose intervals on the Hb value over time ($P = 0.01$), but showed that both HD and older patients required more frequent dosing ($P < 0.0001$ and $P = 0.01$, respectively), although the dose amount was not different in any group based on age or mode of renal replacement therapy.

As outlined in CPR 3.1.3.1, the psychological impact of frequent and painful injections also is important to assess when deciding on a dosing frequency in children. Use of less-frequent dosing strategies is, in theory, of benefit by reducing both the absolute number of injections and the pain associated with injections for the child on ESA treatment. However, this may be mitigated by the fact that currently, the only long-acting ESA on the market produces a noticeably increased degree of pain at time of injection for many children compared with some of the short-acting ESA therapies.

At present, there are no good data from the pediatric ND-CKD population with regard to the dosing frequency of various ESAs.

Finally, the Work Group also was aware of results from a soon-to-be-published open-label multicenter noninferiority trial examining the use of darbepoetin alfa versus epoetin alfa in the treatment of anemia in children with CKD stages 4 to 5, including patients on HD and PD therapy and the nondialysis CKD population (Bradley Warady, personal communication, June 7, 2005). Because the results were not yet peer reviewed or published at the time the guidelines were finalized and were not blieved to alter the guideline statements, this study is not incorporated in this set of guidelines, but will provide data related to use of darbepoetin alfa in children.

# CPR FOR PEDIATRICS 3.2: USING IRON AGENTS

Anemia therapy in patients with CKD requires effective use of iron agents, guided by appropriate testing of iron status. Efficacy of iron therapy appears not to be limited to patients with evidence of iron deficiency. (See Guideline 1.2 for diagnosis of iron deficiency.) Thus, the goals of iron therapy are to avoid storage iron depletion, prevent iron-deficient erythropoiesis, and achieve and maintain target Hb levels.

**3.2.1 Frequency of iron status tests: (*FULLY APPLICABLE TO CHILDREN*)**

**In the opinion of the Work Group, iron status tests should be performed as follows:**

**3.2.1.1 Every month during initial ESA treatment.**

**3.2.1.2 At least every 3 months during stable ESA treatment or in patients with HD-CKD not treated with an ESA.**

**3.2.2 Interpretation of iron status tests: (*FULLY APPLICABLE TO CHILDREN*)**

**In the opinion of the Work Group, results of iron status tests, Hb level, and ESA dose should be interpreted together to guide iron therapy.**

**3.2.3 Targets of iron therapy: (*APPLICABLE TO CHILDREN, BUT NEEDS MODIFICATION*)**

**In the opinion of the Work Group, sufficient iron should be administered to generally maintain the following indices of iron status during ESA treatment:**

**3.2.3.1 <u>ADULT CPR</u> HD-CKD:**

- **Serum ferritin > 200 ng/mL, *AND***
- **TSAT > 20%, or CHr > 29 pg/cell.**

**<u>PEDIATRIC CPR</u>**

***HD-CKD:***

- **Serum ferritin > 100 ng/mL; *AND***
- **TSAT > 20%.**

**3.2.3.2 ND-CKD and PD-CKD:**

- **Serum ferritin > 100 ng/mL *AND***
- **TSAT > 20%.**

**3.2.4 Upper level of ferritin: (*FULLY APPLICABLE TO CHILDREN*)**

**In the opinion of the Work Group, there is insufficient evidence to recommend routine administration of IV iron if serum ferritin is greater than 500 ng/mL. When ferritin level is greater than 500 ng/mL, decisions regarding IV iron administration should weigh ESA responsiveness, Hb and TSAT level, and the patient's clinical status.**

**3.2.5 Route of administration: (*FULLY APPLICABLE TO CHILDREN*)**

**3.2.5.1 The preferred route of administration is IV in patients with HD-CKD. (*STRONG RECOMMENDATION*)**

**3.2.5.2 In the opinion of the Work Group, the route of iron administration can be either IV or oral in patients with ND-CKD and PD-CKD.**

**3.2.6 Hypersensitivity reactions: (*FULLY APPLICABLE TO CHILDREN*)**

**In the opinion of the Work Group, resuscitative medication and personnel trained to evaluate and resuscitate anaphylaxis should be available whenever a dose of iron dextran is administered.**

## BACKGROUND

As in adults, the most commonly identified reason for poor responsiveness to ESA therapy in children is iron deficiency.[341]

The need for iron supplementation in children to maintain iron stores and promote the efficient use of ESAs can be predicted from the knowledge of mean daily blood—hence iron—losses in both those who are predialysis and those on dialysis therapy. Predialysis patients, and likely those on PD therapy, lose on average 6 mL/m$^2$/d of blood, mainly from the GI tract, which translates to a cumulative yearly iron loss and therefore requirement of 0.9 g/1.73 m$^2$.[342] This is just

more than half of that predicted for pediatric HD patients, for whom the mean GI blood loss is 11 mL/m$^2$/d, and when coupled with the dialyzer losses of 8 mL/m$^2$ per treatment, translates to a yearly cumulative loss of approximately 1.6 g/1.73 m$^2$.[342]

As in the adult population, several studies have shown that supplementation of iron in children receiving ESA therapy allows a reduction in the ESA dose required per unit of Hb level achieved.[343,344] However, constipation and nausea, as well as poor GI iron absorption, often limit effective supplementation with oral iron preparations.[166,345,346] These facts and the availability of newer IV iron preparations believed less likely to induce AEs recently led to more studies with IV preparations of iron in children. The majority of these studies examined only patients in CKD stage 5, especially those on HD therapy.[304,305,344,347,348]

## RATIONALE

### *Frequency of Iron Tests*

This guideline is considered applicable to children because there are no special data in the pediatric population and there is no reason for a different recommendation.

### *Interpretation of Iron Tests*

This guideline is considered applicable to children because there are no special data in the pediatric population and there is no reason for a different recommendation.

### *Targets of Iron Therapy*

#### *HD-CKD*

Caution must be exercised in applying the targets or normal ranges as outlined in the guideline for adult patients with HD-CKD because the increase in ferritin target from 100 to 200 ng/mL in adult HD patients is based on evidence to suggest that a level of 100 ng/mL underestimates iron deficiency,[98,99,151–156] and data from a study in which patients with an average serum ferritin level of 730 ng/mL showed a 40% reduction in ESA dose compared with those with an average ferritin level of 297 ng/mL.[108] There is no similar RCT-level evidence for this in children; namely, that achieving a specific ferritin level will produce a consistent decrease in ESA doses required, and there are no adult or pediatric data on the safety of supraphysiological ferritin levels.

One pediatric study in older children on HD therapy suggested that a TSAT less than 20%, but not a ferritin level less than 100 ng/mL, was predictive of iron deficiency.[349] However, other pediatric studies in the CKD population have shown that although a normal ferritin level cannot exclude iron deficiency, absolute or functional,[348,350] a low ferritin level, less than 60 ng/mL, is a specific predictor of its presence.[351]

Therefore, we recommend that the current Guidelines be followed in children with the exception that until data are available on the risks and benefits of higher ferritin targets in children, the targets be left at a ferritin level greater than 100 ng/mL and TSAT greater than 20% for patients with HD-CKD, as well as PD-CKD and ND-CKD populations.

With respect to the use of CHr, which has been touted as a valuable screening test for iron deficiency in "normal" children even before the appearance of iron-deficient anemia, the cutoff normal and abnormal values remain unclear and wide. For example, a cutoff value of 26 pg only produced sensitivity and specificity of 70% and 78% for iron deficiency and 83% and 75% for iron deficient anemia in this select group of non-CKD young children, respectively.[352]

In the pediatric CKD literature, CHr has been examined in a limited fashion in children on HD therapy.[304,305] In both studies, an increase from baseline CHr levels was observed in response to oral iron, IV iron dextran, and IV sodium ferric gluconate in patients judged to be both iron replete (oral iron and IV iron dextran)[304] and iron-deficient (IV sodium ferric gluconate).[305] Unfortunately, cutoff values for use of this marker in the pediatric CKD population are not clear, and this is shown clearly in these 2 studies, in which, in nearly identical patient populations (ie, children on HD therapy), the baseline value for CHr was higher in the group judged as iron deficient based on current DOQI guidelines[305] than in those judged iron-replete by those same criteria.[304]

Therefore, whereas it is clear that CHr may yet have a prognostic or diagnostic role in anemia in children with CKD, further research clearly is

needed to understand and define the value of this test in the pediatric CKD population.

*ND-CKD and PD-CKD*

This guideline is considered applicable to children because there are no special data in the pediatric population and there is no reason for a different recommendation.

*Upper Level of Ferritin*

This guideline is considered applicable to children because there are no special data in the pediatric population and there is no reason for a different recommendation.

Note: As in the adult guidelines, this refers only to the intentional targeting of a patient's ferritin level to greater than 500 ng/mL, not to the individual's achieved or acquired ferritin level, which may be at or greater than this level.

*Route of Administration*

This guideline is considered applicable to children because there are no special data in the pediatric population and there is no reason for a different recommendation.

Suggestions for iron supplementation in children with CKD vary in terms of dose, as well as type of preparation. Many children in the ND-CKD or PD-CKD populations may benefit from and receive oral iron therapy,[325] whereas those on HD therapy are likely to require and most often receive IV agents to allow for sufficient iron stores for ongoing erythropoiesis.[325,348,350]

*Oral Iron*

For oral iron therapy, the recommendations are for doses of elemental iron ranging from 2 to 3 mg/kg/d up to 6 mg/kg/d, with a maximum of 150 to 300 mg of elemental iron per day in 2 to 3 divided doses[335,336] taken 2 hours before or 1 hour after all calcium-containing binders and food to maximize GI absorption.[353] A prospective randomized trial of 35 pediatric patients between 1 and 20 years of age on HD therapy, all iron replete, examined response to oral or IV iron (more details discussed next).[304] This study clearly showed a much better response to IV iron in terms of an increased serum ferritin level, but did not show any advantage of IV over oral iron in terms of maintaining iron stores.

*Efficacy of IV Iron*

To date, the largest randomized prospective study to address this issue is a multicenter, international, double-blind, parallel-group, efficacy and safety study that examined the use of sodium ferric gluconate in anemic children with a mean age of 12.1 $\pm$ 2.6 years on HD therapy.[305] All patients at the time of enrollment met 1 or both of the current KDOQI targets for iron deficiency while on ESA therapy, ie, a TSAT less than 20% or ferritin level less than 100 ng/mL. Of this group, data from 56 patients were available to assess the efficacy of the 2 dosing regimens chosen: 1.5 versus 3.0 mg/kg administered for 8 sequential HD sessions.

All patients in both dosing arms showed a significant increase in their baseline Hb levels of 0.9 g/dL at 2 weeks; 0.9 g/dL in the 1.5-mg/kg dose and 1.0 g/dL in the 3.0-mg/kg dose arm at 4 weeks from the last dose of IV iron, all $P < 0.02$. No patient had any change in rHuEPO dose during the iron therapy; however, during the 4-week follow-up period, 5 patients had reductions in rHuEPO dose of 14%, 20%, 50%, 50%, and 67%, all at the 2-week point. Evaluation of all other indices studied (TSAT, ferritin level, and CHr) also showed a significant mean increase from baseline values in both arms, which remained significant at 4 weeks after infusion. However, only ferritin levels showed a significant change between the low-dose and high-dose iron arms, seen at both the 2-week and 4-week time points following the last dose of IV iron. Based on their data, the investigators concluded that IV sodium ferric gluconate was efficacious in both repleting and maintaining iron stores in children on HD up to 4 weeks after infusion.

In a separate and earlier randomized prospective study, the investigators studied 35 pediatric patients between 1 and 20 years of age on HD therapy for their response to oral or IV iron.[304] All patients were iron replete, as defined by KDOQI, with a TSAT greater than 20% and ferritin level greater than 100 ng/mL. They were all well dialyzed and randomized to either weekly IV iron dextran, which was dosed by weight and provided as 2 sets of 6 weekly doses with two 2-week breaks to monitor levels, or daily oral iron at a dose of 6 mg/kg/d as outlined in the NKF-KDOQI 2000 Anemia Guidelines for 16

weeks.[2] Data showed that only the IV iron dextran produced a significant increase in serum ferritin levels, $P = 0.001$. Those treated with IV iron dextran also showed a significant decrease in dose of rHuEPO required to maintain target Hb levels, $P = 0.046$, and an increase in CHr, although this was not statistically different from those seen in the oral iron group. Both the oral and IV preparations maintained all patients in the iron-replete state, as when the study was started. Although there was a significant difference in mean ferritin levels (259.1 compared with 138.5 ng/mL; $P = 0.003$) and rHuEPO doses (reduction of 33% from baseline; $P = 0.046$) in the IV iron group during the study, there was no statistically significant difference between the IV versus oral iron arms as a whole. The investigators concluded from this short-term study that IV iron dextran seemed more effective in improving—but no more effective in maintaining—iron stores in pediatric HD patients on ESA therapy compared with oral iron.

Another prospective randomized trial examined the issue of intermittent versus maintenance IV iron in pediatric patients on HD therapy.[347] The study group of 20 patients received IV iron dextran targeted to initial ferritin levels and a calculation of the net projected iron stores required to target an Hb level of 11.55 g/dL, whereas the 20 patients in the control group were treated with intermittent courses of 10 weekly doses of IV iron dextran as defined by body weight (repeated as necessary based on the presence of a ferritin level $<$ 100 ng/mL, TSAT $<$ 20%, or Hct $<$ 33%). All patients had basal Hb levels of approximately 8 g/dL and reached 10 g/dL by 3 months in both arms. The study's end points were ferritin, TSAT, and Hb levels. Success was defined as maintaining an acceptable target range of ferritin between 100 and 800 ng/mL and TSAT of 20% to 50%. The study enrolled both absolute and functionally iron-deficient patients. A large number of patients, 20, were excluded during this study; 13 patients because of iron overload, defined as a ferritin level greater than 800 ng/mL (9 from the control group). Three patients in the control group required a blood transfusion and also were excluded. Using the study's iron and rHuEPO protocols, there was a significant difference in iron dose required during the study, 6 mg/kg/mo (95% CI, 3.3 to 8.8) in the study group compared with 14.4 mg/kg/mo (95% CI, 12 to 16.8) in the control arm, $P < 0.001$. The investigators showed that patients in the study arm achieved and maintained a stable Hb value, whereas those treated as controls had a much more variable increase and decrease in Hb values.

Four other nonrandomized trials in children,[344,348,350,354] all involving HD patients and 1 including patients with ND-CKD and/or transplant recipients,[354] examined the utility of IV iron in maintaining or increasing Hb levels and decreasing the dose of ESA required to do so. Two trials used iron gluconate,[350,354] 1 trial used iron dextran,[348] and 1 trial used iron sucrose[344]; doses ranged from 1 to 4 mg/kg/wk of the various products as maintenance therapy, and time of therapy varied from 2 to 24 weeks. All 4 trials showed increases in either Hb level or Hct and a decrease in ESA requirements between 5% and 62% per week or per dose of ESA.

A recent meta-analysis on the use of IV iron in pediatric HD patients used pooled data that did not include the 2 most recent trials,[304,347] but included the other 4 studies described, as well as a number of abstracts. Meta-analysis showed that in terms of an increase in Hb, Hct, ferritin, and TSAT values and decrease in ESA requirements, there was a positive correlation with IV iron therapy with an effect size that varied from 0.62 (95% CI, 0.11 to 1.13) to 1.86 (95% CI, 1.58 to 2.15) when evaluated using a standardized weighted-mean difference approach.[343]

### *Dosing of IV Iron*

The use of IV iron preparations and the appropriate dosage of each is a complex topic. It is made more so because one needs an approach to both the immediate repletion of iron stores in a patient who is deficient and a strategy for maintaining an effective level of iron for ongoing erythropoiesis.

The goal of the initial iron therapy is to replenish the body store of functional iron and thus assist in the production of red blood cells and Hb in concert with an ESA. The exact dosing regimens, frequency of IV iron therapy, and appropriate monitoring for effectiveness and safety will be related to the iron preparation chosen.[2,305,344,355]

Currently published pediatric studies looking at the issue of chronic or maintenance therapy

with IV iron have provided 1 to 2 mg/kg/wk of elemental iron and targeted TSATs between 20% and 50% and serum ferritin levels of 100 to 800 ng/mL, based on the prior Anemia Guidelines,[2] to decide on further doses and frequency of administration.[344,350]

It is important to remember that it is possible to have acceptable levels of both TSAT and ferritin and still benefit from IV iron if the patient has so-called functional iron deficiency; therefore, occasionally, after careful assessment of the risk and benefits, a "trial" of IV iron in an anemic patient—even one who appears iron replete—may be indicated.

*Use of IV Iron in Patients with ND-CKD and PD-CKD*

The issue around the utility and practicality of using IV agents in the non-HD population needs to be addressed in children because it is not uncommon that these patients either show an inability to tolerate or fail to respond to oral replacement of iron stores.

Currently, in pediatrics, the lack of easy IV access hampers the use of the strategies used in the HD population, namely, small, but frequent, dosing. In the non-HD population, much higher single doses of the various IV irons, such as dextran,[356–358] sucrose,[359,360] or gluconate,[361] have been administered at less frequent intervals (eg, monthly) in adults to obtain the benefit of IV therapy while minimizing the inconvenience of both the need for IV starts and hospital monitoring during the therapy. However, this may carry different risks in terms of either acute or chronic toxicities. Currently there is little comparable evidence in children, with only 1 published study reporting a maximum delivered dose of iron sucrose of 200 mg[344] and another reporting a maximum dose of 250 mg of iron gluconate.[354]

*Safety of IV Iron*

One concern in the use of IV iron in children, especially in an outpatient setting, is the potentially fatal acute AEs.[179] All forms of IV iron may be associated with acute AEs, which may include hypotension, anaphylactoid reactions, and a variety of other symptoms. Immune mechanisms with activation of mast cells or release of bioactive partially unbound iron into the circulation resulting in oxidative stress and hypotension (labile or free iron reactions) are both possible mechanisms, and the underlying cause may differ depending on the type of IV iron. Anaphylactoid reactions appear to occur more frequently with iron dextran,[173] and labile or free iron reactions, more frequently with nondextran forms of iron.[174] (For further discussion, please see the corresponding Adult Guidelines.)

Although very rare in pediatrics, of 28 children enrolled in 2 separate studies involving iron dextran,[304,348] 1 child had an allergic reaction that necessitated stopping the medication.[348] Current evidence would suggest that the risk for life-threatening reactions is greater with IV dextran products than sodium ferric gluconate[175] and iron sucrose products.[187]

Although both iron sucrose and gluconate products seem to have better safety profiles than dextran, side effects—presumably caused by acute iron toxicity during rapid free iron release—also have been described with both of these products.

With respect to sodium ferric gluconate, pediatric safety data from the trial described earlier[305] were available in 66 patients administered 8 IV doses. One patient in the group administered 1.5 mg/kg per dose was reported to have isolated episodes of mild nausea, diarrhea, and vomiting, whereas a patient in the 3.0-mg/kg group had an episode of severe anemia ascribed to the drug by the investigator at that site. However, no patient had an allergic or anaphylactic reaction during the immediate treatment; no delayed reactions occurred in the 4 weeks after the last iron dose, and no deaths were reported during the study. Together with data from 2 other trials in which 21 children were administered this product without serious AEs, this observation offers some proof about the safety of sodium ferric gluconate in children.[350,354]

Iron sucrose safety data are sparse in the pediatric CKD literature, with only 2 studies reported. One was a retrospective study that did not report serious AEs in the 8 patients who had received at least 1 dose of IV iron sucrose as Venofer (American Regent, Shirley, NY).[344] Another was a prospective trial that looked at only a small number of patients (n = 14) divided into 3 different treatment groups with various iron regimens and did not specifically report on AEs.[362]

The issue of iron overload as a "side effect" of IV iron therapy also should be addressed. Iron excess is believed to generate cellular oxidative stress, and iron stored as ferritin can assist in initiating lipid peroxidation of cell membranes.[363] In humans, increased ferritin levels have been linked to a variety of conditions, including increased severity of strokes[364] and acute renal failure,[365] although direct evidence for tissue toxicity related to serum ferritin level is lacking in the CKD population.

In children, a study comparing 2 different dosing strategies of iron dextran showed, by using Kaplan-Meier analysis, a hazard of iron overload (defined by the investigators as a serum ferritin level $>$ 800 ng/mL or TSAT $>$ 50% at any time during the trial) of 20% in the study arm versus 100% in the control arm after 6 months of treatment.[347] Patients with functional iron deficiency also were statistically more likely to develop iron overload than those with an absolute iron deficiency, 70% versus 19%; $P < 0.005$. Note: There was no direct or indirect evidence of organ damage offered by the investigators in support of their definition of iron overload.

Finally, the Work Group also was aware of results from a soon-to-be-published prospective multicenter trial of sodium ferric gluconate complex for maintenance iron therapy in iron-replete children on HD therapy and administered rHuEPO (Bradley Warady, personal communication, June 7, 2005). Because results were not yet peer reviewed or published at the time these guidelines were finalized and were not believed to alter the guideline statements, the study is not incorporated in this set of guidelines, but will provide data related to dosing, safety, and efficacy of rHuEPO in the pediatric HD-CKD population.

# CPR FOR PEDIATRICS 3.3: USING PHARMACOLOGICAL AND NONPHARMACOLOGICAL ADJUVANTS TO ESA TREATMENT IN HD-CKD

Several pharmacological agents and nonpharmacological manipulations of the HD prescription have been examined for potential efficacy as adjuvants to ESA treatment. Studies are not available to address the use of pharmacological or nonpharmacological adjuvants to ESA treatment in patients with ND-CKD and PD-CKD.

**3.3.1 L-carnitine:** ***(FULLY APPLICABLE TO CHILDREN)***

**In the opinion of the Work Group, there is insufficient evidence to recommend the use of L-carnitine in the management of anemia in patients with CKD.**

**3.3.2 Vitamin C:** ***(FULLY APPLICABLE TO CHILDREN)***

**In the opinion of the Work Group, there is insufficient evidence to recommend the use of vitamin C (ascorbate) in the management of anemia in patients with CKD.**

**3.3.3 Androgens:** ***(FULLY APPLICABLE TO CHILDREN)***

**Androgens should not be used as an adjuvant to ESA treatment in anemic patients with CKD.** ***(STRONG RECOMMENDATION)***

## RATIONALE

### *L-carnitine*

This guideline is considered applicable to children because there are no special data in the pediatric population and there is no reason for a different recommendation.

There are only a few small studies published addressing the topic of L-carnitine in children. Pediatric patients on HD therapy may have low plasma carnitine levels[366-368]; this is less clear in pediatric PD patients, for whom the data are more conflicting.[369,370] However, any justification for use of L-carnitine in children is much sparser than in the adult literature.

One extremely small trial in which 2 children on HD therapy were administered IV L-carnitine showed an increase in their Hct by 34% with no change in erythropoietin dose delivered.[371]

A relatively small study of 16 pediatric dialysis patients, 11 on HD therapy, administered oral carnitine divided twice daily at a dose of 20 mg/kg/d for 26 weeks and did not show a benefit with respect to increased Hb or Hct values or decreased dose requirement for erythropoietin.[372] There also is indirect evidence that because the study was not designed to look at Hb or Hct levels, achieving much higher serum L-carnitine levels using a 5 times greater oral dose in children on continuous ambulatory PD therapy would not change the Hb levels.[370]

Finally, a word of caution is warranted: there also has been concern expressed over the use of oral carnitine because it may produce toxic metabolites.[202]

### *Vitamin C*

This guideline is considered applicable to children because there are no special data in the pediatric population and there is no reason for a different recommendation.

### *Androgens*

This guideline is considered applicable to children because there are no special data in the pediatric population and there is no reason for a different recommendation.

# CPR FOR PEDIATRICS 3.4: TRANSFUSION THERAPY

Red blood cell transfusions should be used judiciously in patients with CKD, especially because of the potential development of sensitivity, affecting future kidney transplantation. However, despite the use of ESA and iron therapy, transfusion with red blood cells occasionally is required, in particular in the setting of acute bleeding.

**3.4.1** ***(FULLY APPLICABLE TO CHILDREN)*** **In the opinion of the Work Group, no single Hb concentration justifies or requires transfusion. In particular, the target Hb recommended for chronic anemia management (see Guideline 2.1) should not serve as a transfusion trigger.**

## RATIONALE

There is no good evidence to support any different recommendations in children compared with adults with respect to this guideline because the physiological principles underlying this guideline hold true in children with anemia and CKD. The pediatric practitioner also may wish to consider the following evidence.

Currently, there are no specific guidelines related to transfusion of red blood cells in children with any level of CKD, on or off dialysis therapy. However, it should be recognized that any of these children, as with an adult, will benefit most from red blood cell transfusions only in the face of impaired oxygen delivery, ie, not based on an Hb "number." Poor oxygenation is a universally followed indication for transfusions in children older than the neonate who do not have concurrent hematologic symptoms or CVD.[271,373,374]

It also should be remembered that red blood cell transfusions, at least in the critically ill pediatric patient, may not be "benign" therapy. This was highlighted by a retrospective cohort study of 240 children in 5 pediatric intensive care units, 130 of whom received red blood cell transfusions. The study showed that even after controlling for a number of factors, such transfusions were associated with increased use of oxygen, days of mechanical ventilation, vasoactive agent infusions, length of intensive care unit stay, and total length of hospital stay (all $P < 0.05$).[373]

Finally, with respect to transfusions in pediatric patients awaiting renal transplantation, it is possible that the need for or use of packed red blood cell transfusions may benefit the pediatric patient if chosen carefully and provided under immunosuppressive coverage in a planned manner. The most current and largest study involved 193 children, 91 of whom received 2 sequential blood transfusions, either random or donor specific if a living related donation was expected, done 1 month apart under cover of oral cyclosporine.[375] Significant improvements in both 1-year and 5-year graft survival were reported: 96% versus 78% and 90% versus 64% ($P < 0.001$). Whereas not minimizing the risk for transmission of infectious agents from blood transfusions, especially if that transfusion is unnecessary, data suggest further prospective trials of red blood cell transfusion before transplantation might be of value in children.

# CPR FOR PEDIATRICS 3.5: EVALUATING AND CORRECTING PERSISTENT FAILURE TO REACH OR MAINTAIN INTENDED HB LEVEL

Although relative resistance to the effect of ESAs is a common problem in managing the anemia of CKD and is the subject of intense interest, the bulk of available information suggests that—in the absence of iron deficiency—there are few readily reversible factors that contribute to ESA hyporesponsiveness.

**3.5.1 Hyporesponse to ESA and iron therapy: *(FULLY APPLICABLE TO)* CHILDREN**

**In the opinion of the Work Group, the patient with anemia and CKD should undergo evaluation for specific causes of hyporesponse whenever the Hb level is inappropriately low for the ESA dose administered. Such conditions include, but are not limited to:**

- **A significant increase in the ESA dose requirement to maintain a certain Hb level or a significant decrease in Hb levels at a constant ESA dose.**
- **A failure to increase the Hb level to greater than 11 g/dL despite an ESA dose equivalent to epoetin greater than 500 IU/kg/wk.**

**3.5.2 Evaluation for PRCA: *(FULLY APPLICABLE TO CHILDREN)***

**In the opinion of the Work Group, evaluation for antibody-mediated PRCA should be undertaken when a patient receiving ESA therapy for more than 4 weeks develops each of the following:**

- **Sudden rapid decline in Hb level at the rate of 0.5 to 1.0 g/dL/wk, *or* requirement of red blood cell transfusions at the rate of approximately 1 to 2 per week, *AND***
- **Normal platelet and white blood cell counts, *AND***
- **Absolute reticulocyte count less than 10,000/$\mu$L.**

## RATIONALE

### *Hyporesponsiveness to ESA and Iron*

This guideline is considered applicable to children because there are no special data in the pediatric population and there is no reason for a different recommendation.

### *Definition of Hyporesponsiveness*

The principles outlined in the adult guideline should be kept in mind when assessing a child who appears to have hyporesponsiveness to ESA therapy; however, the indications as outlined in Guideline 3.5.1 may not be directly applicable to children because there are no published data from which we can confidently define an excessive epoetin dose to maintain a given Hb target.

In terms of the mean ESA dose required, it is clear from the NAPRTCS 2004 annual report that in all children, the average dose never appears to exceed approximately 350 U/kg/wk, even in the youngest children and even during up to 30 months of follow-up.[325] What is not clear is what the upper limit of this dose is in children who seem to respond with an increase in Hb level; hence, it is not currently feasible to set an upper limit dose that, if exceeded in a child whose Hb level is persistently less than 11.0 g/dL, should trigger a consideration for the presence of hyporesponsiveness, although the target in children younger than 5 years would intuitively be greater than that set in the adult guidelines.

### *Potentially Treatable Disorders*

In terms of the factors outlined in the adult guideline as being associated with persistent failure to achieve target Hb levels, these are relevant to children as well, and in a retrospective review of 23 patients on HD therapy for more than 6 months, it was shown that there appeared to be a relationship between the need for high doses of rHuEPO (defined as $>$ 450 U/kg/wk) in patients who were younger, weighed less, had greater parathyroid hormone levels, and had more episodes of bacteremia (all $P < 0.03$).[341] An unexpected finding in this study, relating a high serum ferritin level to an increased risk for hyporesponsiveness, likely (as suggested by the investigators) was related to the presence of inflammation in patients with more frequent episodes of bacteremia.

### *Evaluation for Diagnosing and Treating Antibody-Mediated PRCA*

This guideline is considered applicable to children because there are no special data in the pediatric population and there is no reason for a different recommendation.

A brief review of pediatric PRCA cases is presented next.

A study reviewed all 191 confirmed cases of PRCA up until April 2004, including 3 pediatric patients; an 11-year-old boy from the United States, a 17-year-old girl from Brazil, and a 19-year-old boy from France.[278] Two of these patients, the 11- and 17-year-olds, received only 1 ESA, epoetin alfa (Procrit®; Ortho Biotech Products, LP, Bridgewater, NJ and Eprex®; Ortho Biotech Products, LP, Bridgewater, NJ, respectively) before developing PRCA. The 19-year-old received both epoetin alfa and epoeten beta, Eprex® and Neorecormon® (F. Hoffmann-La Roche, Ltd, Basel, Switzerland). The 11- and 19-year old patients developed PRCA after 18 months of exposure to an ESA, whereas the 17-year-old developed it 7 months after first exposure to an ESA. The latter subsequently died of cardiac arrest 20 months after the original diagnosis; no data about any form of therapy are available. There are no outcome or therapy data available for the 19-year-old patient; however, the 11-year-old received a renal transplant and subsequently "recovered" from PRCA.

Obviously, these numbers are very small and, for practical purposes, suggest a very low risk for PRCA in children compared with the risk inherent in being anemic or requiring repeated blood transfusions. However, it should be recognized that this problem can occur in children and should be part of the differential for a child with a low reticulocyte anemia in the presence of a decreasing Hb level and preserved white blood cell and platelet lines that fail to respond to increased iron and/or ESA therapy.

# IV. CLINICAL PRACTICE RECOMMENDATIONS FOR ANEMIA IN CHRONIC KIDNEY DISEASE IN TRANSPLANT RECIPIENTS

# ANEMIA IN CKD IN TRANSPLANT RECIPIENTS

## BACKGROUND

Anemia is relatively common after transplantation. Regular screening and careful evaluation of the multiple factors that can contribute to anemia after transplantation are recommended.

Table 41 summarizes the key features of posttransplantation anemia (PTA). As in other forms of CKD, the prevalence of anemia in transplant CKD clearly is associated with the level of allograft function. However, a number of other factors unique to transplant recipients may contribute to the development of PTA. There is little information regarding the association of anemia with either graft or patient outcomes. Similarly, there is limited information to suggest that the response to treatment with ESAs differs between patients with CKD with and without a transplant. Although there are reports of increased delayed graft function and hypertension with the use of ESAs, there is insufficient evidence to suggest that these agents should not be used in either the immediate posttransplantation or late posttransplantation period. Conversely, with the existing information, it is recommended that treatment guidelines for management of anemia in the general CKD population be followed in the transplant population.

## INTRODUCTION

Transplant recipients are a subgroup of patients with CKD with unique considerations with regard to anemia management.

Transplant recipients have variable exposure to CKD before transplantation. Patients with functioning transplants include preemptive transplant recipients, recipients with variable exposure to dialysis, and repeat and multiorgan transplant recipients. Consequently, the burden of comorbid disease varies among transplant recipients, and this may have important implications for the severity and management of anemia after transplantation.

Most transplant recipients have decreased kidney function. Among 40,963 transplant recipients studied in the United States between 1987 and 1996, mean eGFR achieved at 6 months after the time of transplantation was 49.6 ± 15.4 (SD) mL/min/1.73 $m^2$.[376] In a study of transplant recipients in the United States between 1987 and 1998, more than 70% of patients with allograft function at 1, 3, and 5 years after transplantation had CKD stage 3 or higher.[377] Transplant function may change over time. Although the mean rate of GFR decline was only 1.66 ± 6.51 mL/min/1.73 $m^2$ per year in a large cohort of long-term kidney transplant recipients, kidney allograft function may change rapidly; thus, frequent evaluation of kidney function and Hb level is desirable.[376]

Transplant recipients differ from most other patients with CKD because they are chronically exposed to immunosuppressive medications that may suppress erythropoiesis. The current KDOQI classification of CKD includes transplant recipients.[4] A recent worldwide consensus statement of KDIGO also confirmed that the CKD classification system should be applied to transplant recipients and suggested to add the index letter

**Table 41. Literature Review of Anemia In Transplant CKD: Key Conclusions**

| Prevalence of Anemia | Pathophysiology | Clinical outcomes | Response to treatment | Side effects of treatment |
|---|---|---|---|---|
| Prevalence varies by time after transplantation and by level of graft function. Relationship between Hb and eGFR may not be the same as that seen in other CKD disorders. | Level of transplant kidney function is important, but other factors, including medications, may decrease erythropoietin production or increase resistance to erythropoietin in patients with stable allograft function. | Evidence linking anemia and anemia treatment with graft or patient outcomes, including survival, cardiovascular disease, & hospitalization is limited. | Transplant patients may be relatively resistant to ESA. The precise mechanisms have not been elucidated. | Evidence is insufficient to determine the relationship, if any, between ESA use and potential adverse events in the transplant CKD patient, including delayed graft function, decline in kidney function, or hypertension. |

"T" to the CKD stage category for these patients.[377A] Although many features distinguish transplant recipients from other patients with CKD, transplant recipients are clearly at risk for anemia because of decreased kidney function.

This section reviews the available information regarding the prevalence, pathophysiology, clinical correlates, and treatment considerations of anemia in kidney transplant recipients. The relevant considerations for anemia management before transplantation and after transplant failure also are discussed.

## PREVALENCE

There is no accepted definition of anemia in transplant recipients, and variable definitions are used in the literature. A second important consideration is that the prevalence of anemia is dependent on the time of observation after transplantation.

During the early posttransplantation period, arbitrarily defined as the first 6 months after transplantation, anemia of varying degrees is very common. The prevalence and degree of anemia during this period are dependent on the pretransplantation Hb level, amount of perioperative blood loss, frequency of blood draws, iron depletion,[378-383] persistence of uremia,[382] endogenous erythropoietin levels,[382,384,385] erythropoietin responsiveness,[382,384-387] and exposure to immunosuppressive agents.[388,389]

The time course of erythropoiesis after transplantation has been studied by a number of investigators,[378-382,385,390,391] and reviews on this subject are available.[389,391,392] A transient early peak of erythropoietin is detectable within the first 24 hours after transplantation, particularly in patients with delayed graft function, and is not associated with a measurable increase in Hb level. Within the first number of days after successful transplantation, a smaller, more sustained erythropoietin peak is detectable. This peak is associated with the subsequent onset of erythropoiesis and recovery of renal anemia during the next several months after transplantation.

The prevalence and degree of anemia in the immediate posttransplantation period also will be dependent on the pretransplantation Hb level. Despite the widespread availability of ESAs, anemia continues to be a significant issue in patients presenting for kidney transplantation. A study found that the prevalence of pretransplantation anemia (defined as Hct $< 33\%$) was 41% in adults.[393] In a study of pediatric transplant recipients, the prevalence of pretransplantation anemia (defined as Hct $>$ 2 SDs less than age-specific means) was 67%.[394] In the Transplant European Survey on Anemia Management (TRESAM), 4 cohorts of prevalent transplant recipients were defined by the duration of transplantation (6 months and 1, 3, and 5 years). Mean pretransplantation Hb levels in these cohorts were 11.9 $\pm$ 1.7 (SD), 11.7 $\pm$ 1.8, 11.2 $\pm$ 1.8, and 10.8 $\pm$ 1.8 g/dL, respectively. The higher mean Hb levels in cohorts that underwent transplantation more recently suggested an improvement in pretransplantation anemia management over time.[395] In a study of adult first deceased-donor transplant recipients in the United States between 1995 and 2000, the prevalence of anemia before transplantation was described among the subset of patients who had Medicare as the primary payer for the 12 months before transplantation and who received ESAs before transplantation. Mean pretransplantation Hb levels recorded in the 6 months before transplantation by transplantation year were: 1995 (n = 2296), 10.5 $\pm$ 0.02 (SE) g/dL; 1996 (n = 2394), 10.7 $\pm$ 0.02 g/dL; 1997 (n = 2694), 10.9 $\pm$ 0.02 g/dL; 1998 (n = 2838), 11.0 $\pm$ 0.02 g/dL; 1999 (n = 2723), 11.4 $\pm$ 0.02 g/dL; and 2000 (n = 2857), 11.6 $\pm$ 0.02 g/dL. The higher Hb levels among patients who underwent transplantation more recently suggested an improvement in pretransplantation anemia management over time. Nonetheless, in 20% of patients, Hb levels decreased to less than the KDOQI target of 11 g/dL.[395A]

Table 42 summarizes the published studies describing the prevalence of PTA. Together, the existing literature indicates that PTA is highly prevalent. The results from the few longitudinal studies showed a very high prevalence of anemia in the early posttransplantation period; anemia appears to be least prevalent 1 year after transplantation and then increases in prevalence with time after transplantation. This increase possibly is related to declining allograft function. The available information suggests that the prevalence of anemia is greater in pediatric compared with adult patients.

**Table 42. Prevalence of PTA by Duration of Posttransplantation Period**

| Author, Year | Location | Adult/ Pediatric or Mean Age | N | Definition of Anemia | Timing of Anemia Determination after Transplantation | Prevalence |
|---|---|---|---|---|---|---|
| Saito, 1998 [396, 397] | Japan | Adult | 60 | Male Hb <12.8 g/dL<br>Female Hb <11.5 g/dL | Cross-sectional | 23% |
| Yorgin, 2002 [393] | US | >18 yr | 128 | Hct <33% | Yearly for 5 yr | Time post-transplant (yr)<br>0 = 43%<br>1 = 12%<br>2 = 12%<br>3 = 14%<br>4 = 18%<br>5 = 26% |
| Mix, 2003 [398] | US | Adult | 240 | Hct <36% | Longitudinal over 5 yr | Time post-transplant (yr)<br>0 = 76%<br>1 = 21%<br>4 = 36% |
| Lorenz, 2002 [399] | Austria | Adult | 438 | Male Hb <13 g/dL<br>Female Hb <12 g/dL | Cross-sectional mean 4.9 yr | 39.7% |
| Winklelmayer, 2004 [400] | US | Adult | 374 | Hct <33% | Cross-sectional<br>Mean 7.7 ± 6.7 yr post-transplantation | 28.6% |
| Vanrenterghem, 2004 [395] | Europe | 48 ±13 yr<br>included children >10 yr | 4,263 | Male Hb ≤13 g/dL<br>Female Hb ≤12 g/dL | 4 cohorts<br><br>6 mo (n = 1003)<br>12 mo (n = 960)<br>3 yr (n = 1254)<br>5 yr (n = 1046) | 38.6% overall<br><br>No significant difference in prevalence among cohorts |
| Yorgin, 2002 [394] | US | Pediatric | 162 | 2 SD below age-specific means | Longitudinal | 67% at transplant<br>84% 1 mo<br>64%-82% between 0-60 mo |
| Shibagaki, 2004 [401] | US | Adult | 192 | Male Hb ≤13 g/dL<br>Female Hb ≤12 g/dL | 6 mo<br><br>12 mo | 6 mo = 41%<br><br>12 mo = 45%<br><br>Hb ≤11 g/dL in women, ≤12 g/dL in men was 19% and 20% at 6 mo and 12 mo |
| Kausman, 2004 [402] | Australia | Pediatric | 50 | Hb <110 g/L<br><br>Severe anemia Hb <100 g/L | Cross-sectional | 60% Hb <110 g/dL<br><br>30% Hb <100 g/dL |

## PATHOPHYSIOLOGY

A number of factors may cause PTA; some are shared with other patients with CKD, whereas others are unique to transplant recipients.[398]

### *Factors Shared With Other Patients With CKD*

In general, the evaluation of PTA should parallel that among nontransplantation patients with CKD. The discussion regarding factors contributing to PTA that are shared with other patients with CKD is limited to the most common considerations and to unique considerations in the transplantation setting.

### *Kidney Function*

Level of allograft function is clearly an important determinant of PTA. In the TRESAM, there was a strong association of anemia with kidney transplant function. Of 904 patients with an $S_{Cr}$ level greater than 2 mg/dL, 60.1% were anemic compared with 29% of those with an $S_{Cr}$ less than 2 mg/dL, $P < 0.01$. In a single-center study of 459 patients at least 6 months after transplantation, prevalences of anemia, defined as an Hb level less than 11 g/dL, among patients with CKD stages 1, 2, 3, 4, and 5 were 0%, 2.9%, 6.6%, 27%, and 33%, respectively.[403]

The association of level of allograft function with Hb level appears to vary with the time of observation after transplantation. One study found that, among patients with an eGFR greater than 90 mL/min/1.73 $m^2$, 11% and 7% of patients had anemia at 6 and 12 months after transplantation, whereas among patients with an eGFR less than 30 mL/min/1.73 $m^2$, at 6 and 12 months after transplantation, 60% and 76% were anemic, respectively.[398] These findings suggest that factors in addition to level of allograft function may be important determinants of anemia, particularly during the early posttransplantation period.

Whether the association between anemia and level of kidney function differs in patients with CKD who did and did not undergo transplantation is uncertain. In a study of 23 renal transplant recipients with stable kidney function, 12 anemic patients were compared with the 11 nonanemic control patients.[386] Of the 12 anemic patients, 10 had low erythropoietin levels suggestive of erythropoietin deficiency, 2 patients had higher than anticipated erythropoietin levels suggestive of

erythropoietin resistance, whereas 5 of 11 nonanemic control patients had higher than expected erythropoietin levels. Thus, there appears to be significant variation in erythropoietin production and responsiveness in transplant recipients, which may alter the association between kidney function and anemia in transplant recipients. Other clinically evident examples of the dissociation between Hb level and kidney function in transplant recipients include posttransplantation erythrocytosis and, as in nontransplantation patients with CKD, the lower incidence of anemia among transplant recipients with polycystic kidney disease.[395]

### *Iron Deficiency*

Iron deficiency may be an important factor in the development of anemia after transplantation.[404] There is limited information regarding the prevalence of iron deficiency after transplantation. In a cross-sectional study of 438 prevalent transplant recipients, the prevalence of iron deficiency, defined as a percentage of hypochromic red blood cells of 2.5% or greater, was 20.1%. In another study of 439 prevalent transplant recipients, 41% of patients had a TSAT less than 20%, whereas 44% had a ferritin level less than 100 ng/mL.[403]

The prevalence of iron deficiency may be greater in the early transplantation period because of low pretransplantation iron stores in dialysis patients and increased iron utilization with the onset of erythropoiesis after successful transplantation.[383] In 1 study, 24 of 51 patients were found to be iron deficient in the early posttransplantation period.[381] In a prospective study of 112 transplant recipients, serum ferritin levels decreased from 109.6 $\mu$g/L (range, 21 to 4,420 $\mu$g/L) at transplantation to 54.9 $\mu$g/L (range, 2 to 1,516 $\mu$g/L) at 6 months after transplantation.[405]

### *Transplant-Specific Factors*

*Acute Rejection*

Early acute rejection is reported to cause a sharp decrease in erythropoietin production and anemia.[406] Insights into the molecular mechanisms involved in the development of anemia during allograft rejection have been elucidated from gene expression studies.[407] Among 4 pediatric renal allograft recipients with acute rejection and anemia, a cluster of 11 genes involved in Hb transcription and synthesis, iron and folate binding, and transport were found to be downregulated. An additional mechanism for the development of anemia during rejection is thrombotic microangiopathy, which may develop during episodes of severe vascular rejection.

*Medications*

***Immunosuppressive medications.*** The use of myelosuppressive medications for immunosuppression and antiviral prophylaxis or treatment may be important factors in the development of anemia after transplantation. Azathioprine and mycophenolate mofetil are myelosuppressive; therefore, anemia caused by these drugs often is associated with leukopenia and/or thrombocytopenia. Very rarely, PRCA may occur with the use of these drugs.[388,408,409]

Calcineurin inhibitors infrequently are associated with anemia. The most common mechanism for PTA associated with the use of calcineurin inhibitors is microangiopathy and hemolysis.[410-414] The immunosuppressant OKT3 also has been associated with hemolytic uremic syndrome (HUS) and microangiopathy.[415,416]

Anemia was a significant AE in a phase III trial in which sirolimus was administered with cyclosporine and corticosteroids.[417] A group reviewed the 10-year experience with sirolimus and reported a dose-dependent association of anemia with the drug in phase I and II trials.[418] The association of sirolimus with anemia also recently was shown in single-center analyses.[419] Sirolimus may inhibit erythropoiesis by interfering with intracellular signaling pathways normally activated after the binding of erythropoietin to its receptor, and sirolimus also may be associated with thrombotic microangiopathy.[419,420]

***Antiviral and antimicrobial medications.*** A number of commonly used antivirals and antibiotics may cause anemia, including ganciclovir and trimethoprim-sulfamethoxazole.

***Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists.*** Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) may be associated with PTA. Anemic patients in the TRESAM had higher odds of receiving ACE inhibitors or ARBs (odds ratio, 1.55; 95% CI,

1.34 to 1.80; $P < 0.001$).[395] In a single-center retrospective study, a significant curvilinear dose-response relationship was identified between ACE-inhibitor dose and Hct.[400] The underlying mechanisms are complex and include inhibition of endogenous erythropoietin production, inhibition of angiotensin II–mediated stimulation of red blood cell precursors,[421] and the generation of an erythropoiesis-inhibiting protein by ACE inhibitors.[422]

*Infections and Malignancy*

Anemia may be a feature of cytomegalovirus (CMV) infection. Parvovirus B19 infection has been reported in transplant recipients with anemia and may cause PRCA.[423,424]

Hemophagocytic syndrome (HPS) is a rare cause of PTA. The syndrome often is caused by infectious or neoplastic disease and is defined by bone marrow and organ infiltration by activated nonmalignant macrophages that phagocytose red blood cells. A retrospective analysis of 17 cases among deceased donor transplant recipients showed that the syndrome developed after a median duration of 52 days after transplantation. Fever was present in all patients and hepatosplenomegaly was present in 9 of 17 patients. Eleven patients had received antilymphocyte globulins in the 3 months before presentation. In 9 patients, HPS was related to viral infections (CMV, Epstein-Barr virus, and human heprus virus 6 and 8); other infections included tuberculosis, toxoplasmosis, and *Pneumocystis carinii* pneumoniae. Posttransplantation lymphoproliferative disease was present in 2 patients. The syndrome has a poor prognosis—8 of 17 patients died despite the use of anti-infectious therapy and tapering of immunosuppression.[425]

*Hemolytic Uremic Syndrome*

HUS may recur after transplantation and can result in allograft loss.[426] De novo HUS may occur associated with the use of cyclosporine, tacrolimus, or OKT3. The syndrome also has been associated with CMV and influenza A infection in transplant recipients.[427,428] The possibility that erythropoietic agents may be beneficial in patients with HUS after transplantation is suggested by observations from the nontransplantation population. Plasma from approximately 75% of patients with sporadic thrombotic thrombocytopenic purpura (TTP)/HUS induces apoptosis in cultured microvascular endothelial cells.[429] The mechanism appears to be linked to induction of Fas (CD95) on cultured endothelial cells because the erythropoietin receptor is expressed on vascular endothelial cells.[430, 431] Erythropoietin prevents lipopolysaccharide-induced apoptosis in cultured endothelial cells, suggesting that erythropoietin may have a protective effect and may be of therapeutic benefit in TTP/HUS in the nontransplantation setting.[432] The use of ESAs after transplantation in patients with HUS warrants further study.

*Hemolytic Anemia Associated With Minor Blood Group A, Group B, Group O Incompatibility*

Blood group A recipients receiving transplants from blood group O donors or blood group AB recipients receiving transplants from either group A or B donors may develop evidence of hemolysis caused by anti-A or anti-B antibodies of the donor or from autoantibodies produced by passenger lymphocytes.[433-435]

## CLINICAL OUTCOMES

There is only limited information regarding the association of anemia with clinical outcomes in transplant recipients.

Transplant recipients are known to be at increased risk for cardiovascular events, particularly during the perioperative period. In a single-center study of 404 transplant recipients with diabetes between 1997 and 2000, patients with at least 1 monthly Hct level less than 30% during the first 6 months after transplantation had a significantly greater incidence of cardiovascular events compared with patients with monthly Hct values greater than 30%. In a multivariate analysis that also included patient age and history of ischemic heart disease (IHD), an increase in monthly Hct to greater than 30% was associated with a significantly lower risk for cardiovascular events (RR, 0.65; 95% CI, 0.33 to 0.91; $P = 0.02$).[436]

Among long-term transplant recipients, there is limited information regarding the association of anemia with adverse cardiovascular events. In a retrospective study of 638 transplant recipients between 1969 and 1999 who were alive and free of cardiac disease 1 year after transplantation, lower Hb levels were associated with an increased risk for de novo CHF (RR, 1.24/10-g/dL

decrease in Hb; 95% CI, 1.10 to 1.39; $P = 0.001$).[437] In a follow-up study, anemia was associated with increase in left ventricular mass (as measured by Cornell voltage on electrocardiogram) during the first 5 years after transplantation.[438]

In a recent study, 438 prevalent transplant recipients were followed up for a median of 7.8 years. Laboratory parameters obtained during a 4-week enrollment period in 1995 were tested for their association with all-cause mortality and allograft failure.[439] The investigators did not identify an association between anemia (Hb $<$ 10 g/dL) and all-cause mortality or graft survival. Compared with patients with hypochromic red blood cells less than 5%, patients with hypochromic red blood cells greater than 10% had an RR of 2.06 for all-cause mortality (95% CI, 1.12 to 3.79; $P = 0.02$).

In a retrospective single-center study of resource utilization among 220 kidney transplant recipients, patients with a higher Hct had a decreased risk for hospitalization (RR, 0.95/1% increase in Hct; 95% CI, 0.92 to 0.98; $P < 0.001$).[440]

## RESPONSE TO TREATMENT WITH ESAs AND SAFETY OF TREATMENT

### *Use of ESAs Before Transplantation*

The issue of whether ESA use before transplantation is associated with delayed graft function after transplantation has largely been dispelled by the decreased incidence of delayed graft function in registry data over time despite the increased use of ESAs. A few small retrospective studies had suggested that ESA use may be associated with delayed graft function, presumably because of altered intrarenal blood flow during rewarming in patients with a higher Hct.[441,442] Previous treatment with ESAs does not blunt the production of endogenous erythropoietin after transplantation or the ability to respond to endogenous erythropoietin.[391,443]

### *Early Posttransplantation Period*

Erythropoietic agents are effective in correcting anemia during the early posttransplantation period. Two small prospective randomized studies to study the efficacy of ESAs during the immediate posttransplantation period have been performed.

One study randomized 14 transplant recipients to receive and 15 patients not to receive an ESA.[387] The ESA (150 U/kg/wk) was started at an Hct less than 30% and was increased at weekly intervals by 30 U/kg/wk as long as Hct remained at less than 25%. Hct increased from a nadir of 22% $\pm$ 4% 2 weeks after transplantation to 30% $\pm$ 4% at week 4 and 36% $\pm$ 4% at week 6 ($P < 0.001$ and $P < 0.0001$ versus week 2, respectively). Corresponding values in the non-ESA group were 25% $\pm$ 6%, 28% $\pm$ 6% ($P =$ NS), and 32% $\pm$ 6% ($P < 0.05$ versus week 2; overall ESA versus non-ESA, $P = 0.038$ by analysis of variance). The maximum ESA dose after transplantation was more than 2 times higher than that required before transplantation (197.1 $\pm$ 45.1 versus 85.0 $\pm$ 76.0 U/kg/wk; $P < 0.05$). The investigators concluded that ESAs could safely and effectively correct anemia during the first weeks after transplantation despite relative erythropoietin resistance.

In a recent study, patients were randomized to receive (n = 22) or not receive (n = 18) ESA, 100 U/kg 3 times per week, if Hb level was less than 12.5 g/dL.[444] Time to reach an Hb level greater than 12.5 g/dL was 66.5 $\pm$ 14.5 versus 52.6 $\pm$ 23.7 days in the non-ESA and ESA groups, respectively ($P = 0.05$). After 3 months, Hb levels were not different between the non-ESA and ESA groups (12.6 $\pm$ 1.5 versus 12.0 $\pm$ 1.5 g/dL, respectively). In a Cox regression analysis, ESA use (RR, 7.2; $P = 0.004$) and dose (RR, 0.63; $P = 0.04$) were retained as independent variables predicting the time to reach an Hb level greater than 12.5 g/dL. In the ESA group, 14 of 22 patients reached the target Hb level of greater than 12.5 g/dL compared with 12 of 18 patients in the non-ESA group ($P =$ NS). $S_{Cr}$ levels were not different between groups. The investigators concluded that the use of ESAs in the immediate posttransplantation period had no relevant clinical impact on the correction of anemia after transplantation.

Together, these studies suggest that ESAs are effective in correcting anemia after renal transplantation. The dose of ESA required may be higher than that before transplantation. The studies were not designed to determine whether the correction of anemia was associated with im-

provement in clinical outcomes, resource utilization, or QOL. Further, few patients with delayed or impaired graft function were studied. Thus, whether there are clinically relevant benefits to the early correction of anemia after transplantation remains uncertain.

These studies did not report significant AEs associated with the use of ESAs, such as delayed graft function or hypertension. A recent study reported a significantly increased incidence of transplant renal artery stenosis among pediatric transplant recipients administered ESAs during the first week after transplantation. All patients were enrolled in a steroid-free immunosuppression protocol. Results of DNA microarray analysis showed a series of 12 genes that differentiated the patients who developed renal artery stenosis in this setting.[444A]

Erythropoietin modulates the cellular response to stress and may attenuate apoptosis and necrosis in various organs, including the kidney.[445-451] Whether use of erythropoietic agents can minimize ischemic reperfusion injury, as shown experimentally, warrants investigation.

### *Late Posttransplantation Period*

There are only a few uncontrolled studies describing the use of ESAs to treat late PTA.[452-455] In the largest of these studies, in 40 patients with failing renal allografts, mean Hb levels increased from 78.9 ± 10.4 to 102.6 ± 18.4 g/L after 24 weeks of treatment with ESA, 50 U/kg 3 times per week.[453] The increase in Hb level was associated with a significant improvement in QOL measures. Twelve patients returned to dialysis therapy. These patients all had poor allograft function, and the study could not exclude the possibility that treatment with ESA accelerated renal allograft decline. Although no change in systolic or diastolic blood pressure was noted, the need for antihypertensive medications was significantly increased in 18 patients. An increase in hypertension also was noted in another study.[452] In a single-center study, correction of anemia was associated with a decreased rate of decline in allograft function.[456]

Together, these studies suggest that ESAs are efficacious and likely do not accelerate renal decline, but may aggravate hypertension. Whether patients in the late posttransplantation period require higher doses of ESAs to correct anemia compared with nontransplantation patients with CKD is unclear.[457] A decreased response to ESAs among transplant recipients may be anticipated because of the use of myelosuppressive medications, chronic inflammation, or other factors. The propensity of specific immunosuppressive agents to affect the action of ESAs in kidney transplant recipients is unclear. There is an inverse correlation between ESA dose and $C_{Cr}$ in transplant recipients, and a sudden change in Hct in ESA-treated patients may indicate a change in graft function.[453] The response to ESAs is impaired during episodes of allograft rejection.[407,458] In the TRESAM, the median dose among ESA-treated patients was 4,000 IU/wk (mean, 5,831 ± 4,217 IU/wk), but ESA-treated patients had lower Hb values than non–ESA-treated patients, suggesting that the ESA was underdosed and patients were ESA resistant.[395]

### *Posttransplantation Failure*

Patients with allograft failure have a high mortality that is related primarily to CVD. The management of anemia among patients with failing allografts is suboptimal. In a study of patients initiating dialysis therapy after transplant failure in the United States between 1995 and 1998, mean Hct was 27.5% ± 5.9% and 67% had an Hct less than 30%. The use of ESAs at the time of dialysis therapy initiation was infrequent (35%).[459] Anemia management may be more difficult in patients with transplant failure because of the presence of chronic inflammation and relative resistance to ESAs.[460]

# V. APPENDIX 1: METHODS OF EVIDENCE REVIEW AND SYNTHESIS

### *Aim*

The overall aim of the project is to update the 2000 KDOQI CPGs for Anemia of CKD.[2] The Work Group sought to update the guidelines by using an evidence-based approach. After topics and relevant clinical questions were identified, the available scientific literature on those topics was systematically searched and summarized. High-quality or moderately high-quality evidence formed the basis for the development of evidence-based CPGs. When evidence was of low or very low quality or was entirely lacking, the Work Group could develop CPRs based on consensus of expert opinion.

### *Overview of Process*

Update of the guidelines required many concurrent steps to:

- Form the Work Group and ERT that were to be responsible for different aspects of the process
- Confer to discuss process, methods, and results
- Develop and refine topics
- Create draft guideline statements and rationales
- Define exact populations, interventions, predictors, comparisons groups and outcomes of interest and study design and minimum follow-up time criteria (PICOD)
- Create and standardize quality assessment and applicability metrics
- Create data extraction forms
- Develop literature search strategies and run searches
- Screen abstracts and retrieve full articles
- Review articles
- Extract data and perform critical appraisal of the literature
- Tabulate data from articles into summary tables
- Grade quality and applicability of each study
- Grade the quality of evidence for each outcome and assess the overall quality of the evidence across all outcomes with the aid of evidence profiles
- Write guideline recommendations and supporting rationale statements and grade the strength of the recommendations
- Write CPRs based on consensus of the expert Work Group in the absence of sufficient evidence.

### *Creation of Groups*

The KDOQI Co-Chairs appointed the Co-Chairs of the Work Group, who then assembled groups to be responsible for the development of the guidelines. The Work Group consisted of domain experts, including individuals with expertise in adult and pediatric nephrology, hematology, nursing and nutrition, cognitive function, QOL, and CVD outcomes in patients with CKD. Support in evidence review and methods expertise was provided by an ERT contracted by the NKF at the NKF Center for CPG Development and Implementation. The Work Group and the ERT collaborated closely throughout the project.

The first task of the Work Group members was to define the overall topics and goals for the update. Smaller groups of 2 to 4 individuals were formed and assigned to each topic. The Work Group and ERT then further developed and refined each topic and specified screening criteria for PICOD, literature search strategies, and data extraction forms (described next). Work Group members were the principal reviewers of the literature, and from their reviews and detailed data extractions, they summarized the available evidence and took the primary roles of writing the guidelines and rationale statements.

The ERT consisted of individuals (staff, fellows, and research assistants) from Tufts–New England Medical Center with expertise in nephrology and development of evidence-based CPGs. It instructed the Work Group members in all steps of systematic review and critical literature appraisal. The ERT also coordinated the methodological and analytical process of the report; it defined and standardized the method of performing literature searches, data extraction, and

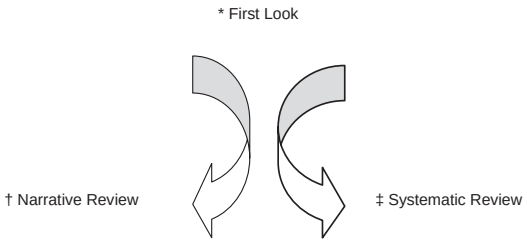


**Fig 19. Process of triaging a topic to a systematic review or a narrative review. *First Look Topic: Topics for which the substance of the evidence base was unclear were first explored to determine their suitability for systematic review. A sensitive Ovid search was performed for each first look topic by the ERT. Abstracts were reviewed by the Work Group members to determine whether there was an adequately defined and sufficient base of scientific information from which to answer the clinically relevant question or resolve controversies. Topics that qualified were submitted to systematic review, while topics lacking a sufficient evidence base for systematic review were summarized by Work Group members in narrative reviews. †Narrative Review: Work Group members had wide latitude in summarizing reviews and original articles for topics that were determined not to be amenable to a systemic review of the literature. Under special circumstances, focused literature search was performed by ERT for a specific subtopic. ‡Systematic Review: A systematic review entailed systematic screening, data abstraction, appraisal, and synthesis of studies in summary tables and evidence profiles.**

summarizing the evidence in summary tables and evidence profiles. It performed literature searches, organized abstract and article screening, created forms to extract relevant data from articles, organized Work Group member data extraction, checked data, and tabulated results. Throughout the project, the ERT conducted seminars and provided instruction on systematic review, literature searches, data extraction, assessment of quality and applicability of articles, evidence synthesis, and grading of the quality of evidence and strength of guideline recommendations.

### *Refinement of Topics and Development of Materials*

The Work Group reviewed the 2000 KDOQI CPGs for Anemia of CKD[2] and determined which of the guideline recommendations required updates and which could remain unchanged. These assessments were based primarily on expert opinion regarding the likelihood of new evidence being available. When experts were uncertain about the current evidence basis of a topic, a "first look" of the topic was undertaken to inform this process (Fig 19). After literature review of potentially relevant abstracts and studies, members of the Work Group focused the specific questions deemed clinically relevant and amenable to systematic review or decided to produce a narrative summary of the literature.

The Work Groups and ERT developed: (1) draft guideline statements, (2) draft rationale statements that summarized the expected pertinent evidence, and (3) data extraction forms requesting the data elements to be retrieved from the primary articles. The topic refinement process began before literature retrieval and continued through the process of reviewing individual articles.

### *Literature Search*

A master reference list was compiled from references used in previous evidence-based guidelines on Anemia and CKD:

1. EBPG II, 2004
2. EBPG I, 2000
3. KDOQI Anemia Guideline Update, 2000
4. DOQI Anemia Guideline, 1997
5. Caring for Australasians with Renal Impairment (CARI) Anemia Guideline, 2003

For the topics addressed in EBPG II, update searches of MEDLINE were performed. For Hb Targets, a module for (Anemia and ESA and Kidney) was run on articles from January 2003 through March 2004. Selective updates of literature searches were performed through November 2004. A pre-MEDLINE search also was performed to capture more recent trials not yet indexed in MEDLINE. For the topic of Iron Targets, the (Anemia and ESA and Kidney) module was modified by adding additional iron terms and was run to include publications between January 2003 and November 2004. For the topics of adjuvants to ESA treatment, a MEDLINE search was conducted for [(Anemia and Kidney) and (Androgens, Statins, Carnitine, Vitamin E, or Ascorbic Acid)] for all articles published from January1989 through September 2004. A separate search for studies on prevalence of anemia by eGFR was conducted from January 1999

**Table 43. Example of a Summary Table**

| Author, Year | N | CKD Stage | Baseline[a] Hb (g/dL) | Follow-up (mo) | Applicability | Arm 1 / Arm 2 / Arm 3 | Mean Hb (g/dL) Target (Achieved) | Clinical Outcomes (Arm 1 vs. Arm 2 vs. Arm 3) | | | | | | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | CVD Events (%) | LVH | Mortality (%) | Hospitalization | Dialysis Adequacy | Transfusion (%) | QOL[b] | |
| *ESA vs. ESA* | | | | | | | | | | | | | | | |
| Besarab, 1998 [108] | 1,233 | HD-CKD | 10.2 | 14 | | ESA High | 14.0 (12.7-13.3) | *Nonfatal MI 3.1 vs. 2.3 NS[c] | — | *29.6 vs. 24.4 NS[c] | NS | ΔKt/V: –0.03 vs. +0.06 P <0.001 | 21 vs. 31 P = 0.001 | See QOL Table | ● |
| | | | | | | ESA Low | 10.0 (10.0) | | | | | | | | |
| Parfrey, 2005 [109] | 596 | HD-CKD | 11.0 | 24 | | ESA High | 13.5-14.5 (13.3) | CVA: 4 vs. 1 P = 0.045 Other CVD: NS | *NS | NS | — | ΔURR: 0 vs. +2 % P <0.05 | — | See QOL Table | ● |
| | | | | | | ESA Low | 9.5-11.5 (10.9) | | | | | | | | |
| Foley, 2000 [110] | 146 | HD-CKD | 10.4 | 11 | | ESA High | 13-14 (13) | NS | *NS | NS | — | Kt/V: LVD: 1.41 vs. 1.50 P = 0.025 | — | See QOL Table | ● |
| | | | | | | ESA Low | 9.5-10.5 (10.5) | | | | | | | | |

through February 2005. The searches also were supplemented by articles identified by Work Group members through September 2005.

Only full journal articles of original data were included. Editorials, letters, abstracts, and unpublished reports were not included. Selected review articles identified in the searches were provided to the Work Group for background material.

MEDLINE search results were screened by members of the ERT for relevance by using predefined eligibility criteria, described in Table 44. Retrieved articles were screened by the ERT. Potentially relevant studies were sent to Work Group members for rescreening and data extraction. Domain experts, along with the ERT, made the final decision for inclusion or exclusion of all articles.

### *Generation of Data Extraction Forms*

Data extraction forms were designed to capture information on various aspects of the primary studies. Data fields for all topics included study setting, demographics, eligibility criteria, causes of kidney disease, numbers of subjects, study design, study funding source, dialysis characteristics, comorbid conditions, descriptions of relevant risk factors or interventions, description of outcomes, statistical methods, results, study quality (discussed later), study applicability (discussed later), and free text field for comments and assessment of biases. Training of the Work Group members to extract data from primary articles occurred during Work Group meetings and by E-mail and teleconference calls. Work Group members then were assigned the task of data extraction of articles.

### *Generation of Evidence Tables*

The ERT condensed the information from the data extraction forms into evidence tables, which summarized individual studies. These tables were created for the Work Group members to assist them with review of the evidence and are not included in this document. All extracted articles and all evidence tables were made available to all Work Group members. During the development of the evidence tables, the ERT rescreened the accepted articles to verify that each of them met the initial screening criteria and checked the data extraction for accuracy. If the criteria were not met, the article was rejected, in consultation with the Work Group.

### *Format for Summary Tables*

Summary tables describe the studies according to the following dimensions: study size and follow-up duration, applicability or generalizability, results, and methodological quality (see Table 43). The ERT generated summary tables by using data from extraction forms, evidence tables, and/or the articles. All summary tables were reviewed by the Work Group members.

In the summary tables, studies were ordered first by method quality (best to worst), then by applicability (most to least), and then by study size (largest to smallest). Results are presented in their appropriate metric or in summary symbols, as defined in the table footnotes.

To provide consistency throughout summary tables, data sometimes were converted or estimated. Follow-up times were converted to months by estimating 1 month as 4 weeks. In general, data provided as percent Hct was converted into grams per deciliter of Hb by dividing by 3. Additionally, results sometimes were estimated

## Table 44. Systematic Review Topics and Screening Criteria

| Topic | Comments |
|---|---|
| **Topic 1.1: Identifying Patients and Initiating Evaluation** | **What is the prevalence of anemia at various stages of kidney function?** |
| Population | All CKD stages |
| Predictor | eGFR, creatinine clearance, CKD stage |
| Outcomes | Prevalence of anemia |
| Study design | Cross-sectional studies |
| **Topic 2.1: Hb Target** | **In CKD patients with anemia of CKD receiving ESA therapy, what are the benefits and harm of treating to higher vs. lower Hb levels?** |
| Population | All CKD stages |
| Intervention | Treat with an ESA to a higher Hb target vs. lower Hb target (with an ESA or placebo/control) |
| Outcomes | All-cause mortality, CVD, LVH, hospitalizations, QOL, progression of kidney disease, dialysis adequacy, hypertension, no. of transfusions, |
| Study design | RCT<br>Minimum ≥2 months follow-up duration. |
| **Topic 2.1: Hb Target** | **What are the AEs associated with treating with ESA to higher vs. lower Hb targets?** |
| Population | All CKD stages |
| Intervention | Treat with an ESA to a higher Hb target vs. lower Hb target (with an ESA or placebo/control) |
| Outcomes | BP change or hypertension, access thrombosis, seizures, any clinically important AEs |
| Study design | Any |
| **Topic 3.2: Using Iron Agents—Optimal Iron Targets** | **Is there an optimal ferritin, TSAT, or CHr level to target with iron therapy to optimize Hb levels or EPO dose in individuals with anemia of CKD?** |
| Population | All CKD stages |
| Intervention | Treat with iron compounds to 2 different levels of ferritin, TSAT, or CHr |
| Outcomes | Change in Hb or ESA dose |
| Study design | RCT |
| **Topic 3.2: Using Iron Agents—Utility of Iron Status Tests** | **How well do different baseline levels or threshold levels of ferritin, TSAT, CHr, or HRC predict that an individual will "respond" to iron administration?** |
| Population | All CKD Stages |
| Predictor | Baseline levels of iron indices (ferritin, TSAT, CHr, or HRC) followed by an intervention of iron administration |
| Outcomes | Change in Hb or ESA dose, change in CHr or reticulocyte index |
| Study design | Prospective studies with prespecified definition of response to iron administration |
| **Topic 3.2: Using Iron Agents—AEs** | **What was the rate of anaphylaxis or serious AEs in individuals naïve to tested IV iron agent?** |
| Population | All CKD stages |
| Intervention | Any IV iron agent |
| Outcomes | Serious AEs as defined by study author. |
| Screening criteria | Studies selected from prior systematic review[190] where N>100 |
| **Topic 3.2: Route of Iron Administration** | **Which is the preferred route of administration for iron therapy, IV or oral?** |
| Population | All CKD stages |
| Intervention | Comparison of treatment of IV vs. oral iron compounds |
| Outcomes | Change in Hb or change in ESA dose |
| Study design | RCT |
| **Topic 3.3: Non-Iron Adjuvants** | **Should one use non-iron adjuvants to ESA therapy: androgens, ascorbic acid, or L-carnitine?** |
| Population | All CKD stages |
| Intervention | Androgens, ascorbic acid, or L-carnitine vs. placebo or control |
| Outcomes | Change in Hb or change in ESA dose |
| Study design | RCT |

**Table 45. Literature Search Yield of Primary Articles for Systematic Review Topics**

| Guideline Topic | Search Strategy | Dates [a] | Abstracts Screened | Full Articles Retrieved | Articles Added by experts | Articles Data Extracted | Articles Included in Summary Tables [b] |
|---|---|---|---|---|---|---|---|
| 1.1: Identifying patients and initiating evaluation | Anemia AND kidney AND GFR | 1999-2005 | 125 | 13 | 3 | 6 | 6 |
| 2.1: Setting Hb targets | Anemia AND kidney AND ESA search as update to master reference list | 2003-2004 | 2,013 | 38 | 2 | 28 | 24 [c] |
| 3.2: Using iron agents | Anemia AND kidney AND ESA AND iron terms search as update to master reference list | 2003-2004 | 1,848 | 50 | 6 | 34 | 9 |
| 3.3: Using pharmacological and nonpharmacological adjuvants to ESA treatment in HD-CKD | Anemia AND kidney AND androgens, statins, carnitine, vitamin E, ascorbic acid | 1989-2004 | 370 | 36 | 8 | 15 | 12 |

a. Additional articles were identified by work group members through September 2005.
b. Does not include articles included in tables other than summary tables.
c. Includes articles that were post hoc analysis of larger studies.

from graphs. All estimated values have been annotated as such.

### *Systematic Review Topics, Study Eligibility Criteria*

The topics covered by systematic review are listed in Table 44. The screening criteria were defined by the Work Group members in conjunction with the ERT.

### *Literature Yield*

For systematic review topics, the literature searches yielded 2,756 citations. Of these, 137 articles were reviewed in full. An additional 19 were added by Work Group members. A total of 83 were extracted and of these, 51 studies are included in Summary Tables. Details of the yield by topic can be found in Table 45.

The literature search yields for first-look topics can be found in Table 46. Upon reviewing the resultant abstracts, only the topics of noniron adjuvants (carnitine, ascorbic acid, and androgens) proceeded to systematic review.

### *Assessment of Individual Studies*

#### *Study Size and Duration*

The study (sample) size is used as a measure of the weight of a study. In general, large studies provide more precise estimates of prevalence and associations. In addition, large studies are more likely to be generalizable; however, large size alone does not guarantee applicability. A study that enrolled a large number of selected patients may be less generalizable than several smaller studies that included a broad spectrum of patient populations. Similarly, longer duration studies may be of better quality and more applicable, depending on other factors.

#### *Applicability*

Applicability (also known as generalizability or external validity) addresses the issue of whether

**Table 45A: Assessment of Study Applicability**

| | |
|---|---|
|  | Sample is representative of the entire target CKD population, or results are applicable to the entire target CKD population, irrespective of study sample. |
|  | Sample is representative of a relevant subgroup of the target CKD population. For example, sample is only representative of target CKD population with clinically active CVD, or only a specific relevant subgroup, such as elderly individuals or incident dialysis patients. |
|  | Sample is only representative of a narrow subgroup of the CKD target population, and not well generalizable to other subgroups. For example, the study includes only a small number of patients or patients on PD with active IHD. Studies of such narrow subgroups may be valuable for demonstrating exceptions to the rule. |

**Table 46. Details of First-Look Topics, Ovid Literature Searches, and Yield by Topic**

| Topic | Search Strategy | Dates | No. of Citations | Relevant Abstracts Submitted to Experts for Review |
|---|---|---|---|---|
| Pediatric patients | Anemia AND kidney AND children | 1989-2004 | 2,101 | 192 |
| Special populations: transplant | Anemia AND kidney AND transplant | 1989-2004 | 680 | 107 |
| Pregnancy | Anemia AND kidney AND pregnancy | 1989-2004 | 206 | 10 |
| Sickle cell/ hemoglobinopathies | Anemia AND kidney AND hemoglobinopathies | 1989-2004 | 582 | 20 |
| HIV | Anemia AND kidney AND HIV/AIDS | 1989-2004 | 228 | 12 |
| Cancer: MM, MDS, etc. | Anemia AND kidney AND cancer | 1989-2004 | 1,557 | 15 |
| Hyporesponsiveness | Anemia AND kidney | 2001-2004 | 1,598 | 46 |
| PRCA | Pure red cell aplasia OR PRCA | 2003-2004 | 188 | 146 |
| Total | | | 7,140 | 548 |

the study population is sufficiently broad so that the results can be generalized to the population of interest at large. The study population typically is defined primarily by the inclusion and exclusion criteria. The target population was defined to include patients with anemia and kidney disease and subdivided into those with CKD stages 3 to 5 not on dialysis therapy and those with CKD stage 5 on HD or PD therapy. Furthermore, topic 3.6 includes such special patient populations as kidney transplant recipients and patients with nonrenal anemias. Applicability was specified for each study according to a 3-level scale (Table 45A). In making this assessment, sociodemographic characteristics were considered, as well as comorbid conditions and prior treatments. Applicability is graded in reference to the population of interest as defined in the clinical question. Target populations are specified in the titles of each summary table (discussed later).

*Study Quality*

Method quality (or internal validity) refers to the design, conduct, and reporting of the clinical study. Because studies with a variety of types of design were evaluated, a 3-level classification of study quality was devised (Table 46A).

*Quality of studies of interventions.* The evaluation of questions of interventions was limited to RCTs. The grading of these studies included consideration of the methods (ie, duration, degree of blinding, number and reasons for dropouts, and so on), population (ie, does the population studied introduce bias?), outcomes (ie, are the outcomes clearly defined and properly measured?), thoroughness/precision of reporting, statistical methods (ie, was the study sufficiently powered and were the statistical methods valid?), and the funding source.

*Quality of studies of prevalence.* The ideal study design to assess prevalence of anemia and its association with eGFR is a cross-sectional study of a population representative of the general population. Criteria for evaluation of cross-sectional studies to assess prevalence are listed in Table 47.

*Results*

The type of results used from a study was determined by the study design, the purpose of the study, and the question(s) being asked for

**Table 46A: Grades for Study Quality**

| | | |
|---|---|---|
| ● | **Grade A** | Least bias; results are valid. A study that mostly adheres to the commonly held concepts of high quality, including the following: a formal study; clear description of the population and setting; clear description of an appropriate reference standard; proper measurement techniques; appropriate statistical and analytical methods; no reporting errors; and no obvious bias. Not retrospective studies or case series. |
| ◎ | **Grade B** | Susceptible to some bias, but not sufficient to invalidate the results. A study that does not meet all the criteria in category above. It has some deficiencies but none likely to cause major bias. |
| ○ | **Grade C** | Significant bias that may invalidate the results. A study with serious errors in design or reporting. These studies may have large amounts of missing information or discrepancies in reporting. |

**Table 47. Evaluation of Studies of Prevalence**

| Evaluation of Validity |
|---|
| Cross-sectional study design |
| Was there a representative and well-defined sample of the population of interest?<br>• Minimize nonresponse<br>• Define sampling strategy<br>• Subgroups defined in advance |
| Were objective and unbiased criteria used to define cases and controls? |
| Were methods for data collection applied equally to all study participants? |
| Was there adjustment for important prognostic factors? |
| **Evaluation of Results** |
| How large is the prevalence of cases? |
| How precise are the estimates of prevalence? |
| Are there important differences among subgroups? |
| **Evaluation of Clinical Applicability** |
| Is the population, or subgroups of the population, under study similar to the population from which my patients are drawn? |
| Were the definitions and measures useful in practice? |
| Are the results useful for estimating probability of disease? |

which the results were used. Decisions were based on the screening criteria and prespecifed outcomes of interest (Table 47).

### *Summarizing Reviews and Selected Original Articles*

Work Group members had wide latitude in summarizing reviews and citing original articles.

### *Guideline Format*

The format for each section containing an evidence-based guideline or a CPR is outlined in Table 48. Each guideline contains 1 or more specific "guideline or statements," which are presented as "bullets" that represent recommendations to the target audience. Implementation issues and research recommendations were formulated after this guideline document had been completed and will be presented in another supplement.

### *Rating the Quality of Evidence and the Strength of Guideline Recommendations*

A structured approach, facilitated by the use of evidence profiles and modeled after the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach,[461] was used to grade the quality of the overall evidence and the strength of recommendations. For each topic, the discussion on grading of the quality of the overall evidence and the strength of the recom-

**Table 48. Format for Guidelines**

| |
|---|
| **Introductory Statement** |
| **Guideline or CPR Statement 1 (strength of recommendation)** |
| **Guideline or CPR Statement 2 (strength of recommendation)** |
| **BACKGROUND** |
| **RATIONALE** |
| **Definitions (if appropriate)** |
| **Strength of Evidence** |
| ***Rationale statement 1*** |
| Supporting text, summary tables and evidence profiles (where applicable) and description of quality of evidence |
| ***Rationale statement 2*** |
| Supporting text, summary tables and evidence profiles (where applicable) and description of quality of evidence |
| **LIMITATIONS** |

**Table 49. Balance of Benefit and Harm**

| |
|---|
| When there was enough evidence to determine the balance of medical benefits and harm of an intervention to a patient, one of th following conclusions were drawn:<br>• There is net benefit<br>• There is no net benefit<br>• There is net harm |
| When there is not enough or not enough good quality evidence to weigh benefit and harm (for example, inconsistency, unclear harm), then the balance of benefit and harm was classified as:<br>• It is uncertain that there is benefit |

mendations was led by the primary expert reviewers of each topic, with participation by the Work Group chairs, all other Work Group members, and the ERT members.

### *Grading the Quality of Evidence*

The quality of a body of evidence pertaining to a particular outcome of interest initially was categorized based on study design. For questions of interventions, the initial quality grade was high if the evidence consisted of RCTs, low if it consisted of observational studies, or very low if it consisted of studies of other study designs. Work Group members decided a priori to include only RCTs for questions of interventions other than harm. The quality rating for each intervention/outcome pair then was decreased if there were some or serious limitations to the quality of the aggregate of studies, there were important inconsistencies in the results across studies, the applicability of the studies to the population of interest was limited or there was uncertainty about the directness of evidence, the data were imprecise or sparse, or there was a high likelihood of bias. The final grade for the quality of the evidence for an intervention/outcome pair could be 1 of the following 4 grades: high, moderately high, low, or very low.

The quality of the overall body of evidence then was determined based on the quality grades for all outcomes of interest, taking into account explicit judgments about the relative importance of each of the outcomes (eg, death and access thrombosis having greater weight than change in ESA dose or Hb level). The actual results were reviewed for each outcome to judge the balance between benefits and harm (Table 49). Four final categories for the quality of overall evidence were used, as shown in Table 50.

Evidence profiles were constructed by the ERT to record decisions about grades and interpretation of summary effects by the Work Group members. These profiles serve to make transparent to the reader the thinking process of the Work Group in systematically combining evidence and judgments. Each evidence profile was filled in by Work Group experts with ERT guidance. Decisions were based on facts and findings from the primary studies listed in corresponding summary tables; additional information related to AEs in nontarget populations, when applicable; and judgments of the Work Group. Judgments about the quality, consistency, and directness of evidence often were complex, as were judgments about the importance of an outcome or the net medical benefit across all outcomes.

The evidence profiles provided a structured approach to grading, rather than a rigorous method of quantitatively summing up grades. In an effort to balance simplicity with full and transparent consideration of the important issues, footnotes were placed to provide the rationale for grading (Table 51).

**Table 50. Definitions of Grades for Quality of Overall Evidence**

| Grade | Definition |
|---|---|
| High | Further research is unlikely to change our confidence in the estimate of effect. |
| Moderately High | Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. |
| Low | Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. |
| Very Low | Any estimate of effect is very uncertain |

**Table 51. Example of an Evidence Profile**

| Outcome | No. of Studies & Study Design | Total N of Patients | Methodological Quality of Studies | Consistency across Studies | Directness of Evidence, including Applicability | Other Considerations | Summary of Findings: Quality of Evidence for Outcome | Summary of Findings: Qualitative Description of Effect Size | Importance of Outcome |
|---|---|---|---|---|---|---|---|---|---|
| Hb/Hct Level / ESA dose | 3 RCTs | 63 | Serious limitations [a] | Important inconsistencies [b] | Direct [c,d] | Sparse data | Very low | No consistent benefit. Only 1 of 3 papers showing significant between-arm comparison in Hb/Hct (difference in Hb of 1.6 g/dL). [c] | Moderate |
| AEs | CKD population: 3 RCTs<br>General population: trials, case reports, narrative reviews | 63+ | Mild to severe AEs noted in RCTs included severe acne, elevated AST [e], discomfort at injection site. This is consistent with reported AEs from androgens in non-CKD populations which include virilization, priapism, peliosis hepatis, liver enzyme abnormalities, and hepatocellular carcinoma. Mechanism of action and profile of AEs of androgens are believed to be similar in non-CKD and CKD populations. | | | | | | High |
| | | | Balance of Benefit and Harm: No Net Benefit | | | | Quality of Overall Evidence: Very Low for Benefit | | |

Footnotes:
a. 1 Grade B and 2 Grade C studies.
b. Statistically significant effect with only 1 of 3 studies.
c. The studies used different ESA and iron protocols and had different definitions for the Hb/Hct outcome.
d. The studies used different ESA and iron protocols and had different definitions for the Hb/Hct outcome.
e. Aspartate transaminase

### *Grading the Strength of the Recommendations*

The quality of evidence for each outcome and across all outcomes was graded in the evidence profile. The guideline recommendation was graded based on the quality of the overall evidence, as well as additional considerations. Additional considerations, such as feasibility, availability of a service, and regional and population differences were implicitly considered. Costs also were considered implicitly, but, in most cases, it was believed that the grading of the evidence and formulation of a guideline and its strength should rest primarily on the evidence for medical benefit to a patient.

The strength of each guideline recommendation was rated as either "strong" or "moderately strong." A "strong" rating indicates "it is strongly recommended that clinicians routinely follow the guideline for eligible patients. There is high-quality evidence that the practice results in net medical benefit to the patient." The "moderately strong" rating indicates "it is recommended that clinicians routinely follow the guideline for eligible patients. There is at least moderately high-quality evidence that the practice results in net medical benefit to the patient." Overall, the strength of the guideline recommendation was based on the extent to which the Work Group could be confident that adherence will do more good than harm. Strong guidelines require support by evidence of high quality. Moderately strong guidelines require support by evidence of at least moderately high quality. Incorporation of additional considerations modified the linkage between quality of evidence and strength of guidelines, usually resulting in a lower strength of the recommendation than would be supportable based on the quality of evidence alone.

After grading the quality of the overall evidence for a topic, the Work Group triaged the recommendations to either an evidence-based guideline recommendation when the quality of evidence was high or moderately high or otherwise to an opinion-based CPR.

In the absence of strong or moderately strong quality evidence or when additional considerations did not support strong or moderately strong evidence-based guideline recommendations, the Work Group could elect to issue CPRs based on consensus of expert opinions. These recommendations are prefaced by "In the opinion of the Work Group," and are based on the consensus of the Work Group that following the recommendations might improve health outcomes. As such, the Work Group recommends that clinicians consider following the recommendation for eligible patients. Issues considered in the grading of the quality of the evidence and the strength of the recommendation are discussed in the Rationale section of each recommendation.

### *Limitations of Approach*

While the literature searches were intended to be comprehensive, they were not exhaustive. MEDLINE was the only database searched, and searches were limited to English-language publications. Hand searches of journals were not performed, and review articles and textbook chapters were not systematically searched. However, important studies known to the domain experts that were missed by the electronic literature were added for consideration.

# WORK GROUP BIOGRAPHIES

**John W. Adamson, MD,** has served as Executive Vice President for Research and Director of the Blood Research Institute of the Blood Center of Southeastern Wisconsin in Milwaukee since 1998. He holds the position of Professor of Medicine (Hematology) at the Medical College of Wisconsin. Before moving to Milwaukee, he was Director of the Lindsley F. Kimball Research Institute of the New York Blood Center since 1989 and President of the Center from 1989 to 1997. Dr Adamson received his MD from the University of California, Los Angeles, after which he trained at the University of Washington in Seattle and at the National Institutes of Health in Bethesda, MD, in the fields of internal medicine and hematology. Before assuming his position in New York, Dr Adamson was professor of medicine and head of the Division of Hematology at the University of Washington. Dr Adamson is a past-President of the American Society of Hematology and past chairman of its committees on scientific affairs and transfusion medicine. Dr Adamson served as a member of the Advisory Council of the National Institute of Diabetes, Digestive and Kidney Diseases of the National Institutes of Health. In 1988, he was designated clinical research professor by the American Cancer Society and elected a Fellow of the American Association for the Advancement of Science. Dr Adamson is past editor-in-chief of *Blood*, past editor of the *Journal of Cellular Physiology*, and founding editor of *Current Opinion in Hematology*. Altogether, he has authored or co-authored more than 400 scientific publications. Dr Adamson has received research funds, grants, or contracts from Watson Pharmaceuticals and Navigant Biotechnologies.

**George R. Bailie, MSc, PharmD, PhD,** is Professor of Pharmacy Practice at Albany College of Pharmacy. He has 20 years of experience in teaching, practice, and research in pharmacotherapeutics and pharmacokinetics in CKD and dialysis. He has published more than 100 original research papers, plus numerous chapters, abstracts, reviews, and cases in the medical and pharmacy literature. He has served on the editorial board and is a regular reviewer for many pharmacy and nephrology journals. Dr Bailie is a member of the Advisory Board for the NKF-KDOQI. He was a member of the KDOQI Work Group that developed the guidelines for Blood Pressure and Antihypertensive Agents in CKD. He is a member of the International Society of Peritoneal Dialysis' Work Group for the Management of Peritonitis. He was designated Fellow of the Royal Pharmaceutical Society of Great Britain for his sustained contributions to the literature of pharmacy and is a Fellow of the American Society of Nephrology. He is a director of Nephrology Pharmacy Associates, Inc, a private consulting company. Dr Bailie has received research funds, grants or contracts from Renal Research Institute, American Regent, Genzyme and Omnicare.

**Jeffrey S. Berns, MD,** earned his MD at Case Western Reserve University, then went on to complete his internship and residency in Internal Medicine at University Hospitals of Cleveland. He did a fellowship in Nephrology and was an Associate Research Scientist in the Department of Physiology at Yale University. Dr Berns recently was promoted to Professor of Medicine at the University of Pennsylvania School of Medicine, where he is Director of Clinical Nephrology and Director of the Renal Fellowship Program for the Renal, Electrolyte and Hypertension Division. Dr Berns was a member of the NKF-DOQI and KDOQI Anemia Workgroup. He has published and lectured on topics related to chronic kidney disease, anemia management in patients with CKD, and other areas in clinical nephrology. He is co-editor of *Drug Prescribing in Renal Failure-Dosing Guidelines for Adults*. He also serves on the editorial board of *Seminars in Dialysis, American Journal of Kidney Diseases*, and *Clinical Journal of the American Society of Nephrology*. He is an active investigator in clinical trials related to anemia treatment in patients with CKD. Dr Berns has received research funds, grants or contracts from Hoffman La Roche, Ortho Biotech, Advanced Magnetics, Inc., and Amgen.

**Kai-Uwe Eckardt, MD** *(Work Group Co-Chair)*, is Professor of Medicine and Chief of Nephrology and Hypertension at the University of Erlangen–Nuremberg, Germany. He received his MD from the Westfälische Wilhelms-Universität Münster, Germany. In 1993, following post-

graduate training in internal medicine, pathology, and physiology, he was appointed Assistant Professor of Physiology at the University of Regensburg, Germany. Subsequently, he continued his training in internal medicine and nephrology at the Charité, Humboldt University in Berlin, where he was appointed Associate Professor of Nephrology in 2000. His major scientific interests are in the molecular mechanisms and physiological/pathophysiological relevance of oxygen sensing and the management of anemia. Professor Eckardt is Subject Editor of *Nephrology, Dialysis and Transplantation* and serves on the editorial board of several other journals. He contributed to the development of the EBPGs for Anemia Management and is a member of the executive committee of KDIGO. Dr Eckardt has received research funds, grants or contracts from the German Research Organization. Additionally, Dr Eckardt has received lecture and consultant fees from Amgen, Roche, Johnson & Johnson, and Affymax. He is also associated with CREATE and TREAT studies.

**Steven Fishbane, MD,** currently is Chief of Nephrology and Associate Chair of the Department of Medicine at Winthrop-University Hospital (WUH) in Mineola, NY, as well as Professor of Medicine at SUNY Stony Brook School of Medicine. He is the Medical Director of WUH Dialysis Network, which includes 4 outpatient dialysis units and 3 hospital units. Dr Fishbane serves as the Chairman of the Long Island Health Network Quality Council; Chairman of the Department of Medicine Quality Improvement Program, WUH; Chairman of Clinical Guidelines Committee, WUH; Co-Chairman of WUH Patient Care Committee; and Associate Chairman of the Department of Medicine, WUH. Dr Fishbane is a member of the Network 2 Medical Review Board. Dr Fishbane has received research funds, grants or contracts from Shire Inc., Amgen Inc., Abbott Labs Inc., Roche Inc., and Watson Inc. Additionally, Dr Fishbane is associated with Ortho Biotech and Watson Pharmaceuticals.

**Robert N. Foley, MD,** was born in Ireland and received his undergraduate MD from University College Cork. He completed Internal Medicine training in Cork, later moving to Saint John's, Newfoundland, Canada, where he completed a residency in nephrology, as well as a Masters in Clinical Epidemiology. From 1999 to 2002, Dr Foley worked at Hope Hospital, Salford, UK, and has been Director, Nephrology Analytical Services, Minneapolis Medical Research Foundation since September of 2002. Dr Foley also is a Co-Editor of the *American Journal of Kidney Diseases*. His major interest is in outcomes research, especially the interplay of cardiovascular and renal disease. Dr Foley is active in anemia correction trials, as well as in the USRDS Cardiovascular Special Study Center. Dr Foley has received research funds, grants or contracts from Ortho Biotech, Amgen and Roche.

**Sana Ghaddar, PhD, RD,** is an Assistant Professor at the American University of Beirut, Lebanon. She has over 10 years experience in the renal and clinical dietetics field. She was one of the renal dietitians at the Peninsula Nephrology Inc., in San Mateo, CA, currently a division of Satellite Healthcare, and has served as a Principle Investigator for two research studies that examined the ability of heme-iron-polypeptide to sustain response to Recombinant Erythropoietin in both hemo and peritoneal dialysis patients. She has presented these and other studies she has been involved in at many national conferences, including National Kidney Foundation, American Dietetics Association and Gerontological Society of America. Dr Ghaddar has received research funds, grants or contracts from the American University of Beirut Research Board. Additionally, Dr Ghaddar is associated with the Kidney Nutrition Education & Life Improvement (K/NELI) study funded by the American Univesity of Beirut.

**John S. Gill, MD, MS,** obtained his MD from the University of British Columbia (UBC) in 1995. He completed his internal medicine training at the University of Western Ontario in 1998 and his nephrology training in 2000 at UBC. He then completed his transplantation training at Tufts–New England Medical Center in Boston and obtained in Masters in Clinical Care Research from Tufts in 2002. Dr Gill currently is assistant professor of medicine in the division of Nephrology at UBC and has a cross appointment at Tuft–New England Medical Center. Dr Gill's research interests focus on clinical outcomes in kidney transplant recipients. He is the principal investigator and co-investigator on current Canadian Institutes of Health Research (CIHR), Kid-

ney Foundation, and Michael Smith Funded studies. Dr Gill is chair of the Canadian Society of Transplantation Work Group for Pan-Canadian database development, member of the Canadian Organ Replacement Register Advisory Board, and member of a number of NKF Committees. Dr Gill received research funds, grants or contracts from the Michael Smith Foundation for Health Research, the Canadian Institute for Health Research, Wyeth Pharmaceuticals, and Roche Pharmaceuticals.

**Kathy Jabs, MD,** is a Pediatric Nephrologist who trained at Babies Hospital, NY, and Children's Hospital, Boston. She has been a faculty member at Children's in Boston (1988 to 1996) and was the Director of Dialysis and Renal Transplantation at Children's Hospital of Philadelphia (1996 to 2000). She currently is the Director of Pediatric Nephrology at Vanderbilt Children's Hospital and an Associate Professor of Pediatrics at Vanderbilt University School of Medicine, Nashville, TN. Dr Jabs has had a long-standing interest in the care of children with CKD. Dr Jabs has received research funds, grants or contracts from King Pharmaceuticals and Watson Pharmaceuticals. Additionally, Dr Jabs is associated with the CKid and FSGS studies sponsored by the NIH.

**Francesco Locatelli, MD,** is Scientific Director and Head of the Department of Nephrology and Dialysis of A. Manzoni Hospital, Lecco, and Postgraduate Professor of Nephrology at Brescia and Milan Universities in Italy. He is past-President of the European Renal Association–European Dialysis and Transplantation Association, Italian Society of Nephrology, and International Society of Blood Purification and was Chairman of the EBPGs.

**Iain C. Macdougall, MD,** is a combined medical and science graduate of Glasgow University, Scotland, from which he was awarded a First Class Honours BSc in Pharmacology in 1980. For the last 10 years, Dr Macdougall has been Consultant Nephrologist and Honorary Senior Lecturer at King's College Hospital in London. He has developed both a clinical and a basic science research interest in factors affecting responsiveness to erythropoietic agents. He has served on the Working Parties responsible for both (1999 and 2004) EBPGs on Renal Anaemia Management, and he currently is a member of the US Anemia Guidelines Working Group, the KDIGO Board of Directors, the Global Scientific Advisory Board for PRCA, and the Council of the European Renal Association. He is frequently invited to lecture both nationally and internationally on this topic, and he has co-authored the section on renal anaemia for the last 2 editions of the *Oxford Textbook of Clinical Nephrology* and the current edition of *Comprehensive Clinical Nephrology*. He also is Subject Editor for *Nephrology Dialysis Transplantation.* Dr Macdougall has received research funds, grants or contracts from Amgen, Hoffman La Roche, Affymax, Vifor, and Johnson & Johnson. Additionally, Dr Macdougall is associated with the CERA (Phase III), OPUS, Hematide (Phase II), TREAT (Phase IV) studies sponsored by Roche, Amgen, Affymax, and Amgen, respectively.

**Patricia Bargo McCarley, RN, MSN, NP,** is a nephrology nurse practitioner at Diablo Nephrology Medical Group in Walnut Creek, California. Ms. McCarley received her BSN and MSN from Vanderbilt University. She is active in ANNA having served on local, regional and national committees. She is currently a member of the Nephrology Nursing Journal Board. Ms. McCarley has authored many publications including most recently chapters in the 2005 ANNA Nephrology Nursing Standards of Practice and Guidelines for Care and the Contemporary Nephrology Nursing: Principles and Practice (2nd Ed.). Dr McCarley has received research funds, grants or contracts from Amgen, Ortho Biotech and Renal Care Group.

**Hans H. Messner, MD,** is the Director of the Blood and Marrow Program at the Princess Margaret Hospital. He has a long-standing interest in exploring the role of transplantation in the management of patients with various hematopoietic diseases. In the laboratory, he has used culture techniques to examine normal and malignant hematopoietic progenitor cell populations. In the recent past, he has been involved in the establishment of a cell-processing facility at the Princess Margaret Hospital that meets the standards of good manufacturing practices (GMP). This laboratory will facilitate clinical skill of cell separation procedures, cell expansions, and vector transactions into relevant cell populations. This technology also will be instrumental in faciliting explorations of regenerative capability of stem

cells for other organ systems. Dr Messner has received research funds, grants or contracts from Ortho Biotech.

**Allen R. Nissenson, MD, FACP,** is Professor of Medicine and Director of the Dialysis Program at the David Geffen School of Medicine at UCLA, where he has developed a comprehensive dialysis program. He is President of the National Anemia Action Council (NAAC) and recently chaired a Chancellor's committee at UCLA on Financial Conflicts of Interest in Clinical Research. He currently is serving on a University of California Task Force on Institutional Conflicts of Interest in Research. Dr Nissenson is Chair of the Faculty Executive Council for the David Geffen School of Medicine at UCLA. He has served as Chair of the Southern California ESRD Network during its organizational years in the early 1980s and recently was elected as President-elect. He is Chair of the Medical Review Board. Dr Nissenson currently is consulting for RMS Disease Management, Inc and for Philtre, Ltd, an organization developing new renal replacement therapies based on the application of nanotechnology to this field. Dr Nissenson served as a Robert Wood Johnson Health Policy Fellow of the Institute of Medicine in 1994 to 1995. He is Immediate Past President of the Renal Physicians Association and has served as a member of the Advisory Group overseeing the entire NKF-DOQI, as well as serving as a member of the anemia Work Group. Dr Nissenson's major research interests focus on the quality of care for patients with CKD. His research has included extensive clinical trials of new devices and drugs related to renal disease. Dr Nissenson is co-principal investigator on a recently obtained National Institutes of Health Center Grant looking at issues of disparities in health care delivery for patients with CKD. He is the author of 2 dialysis textbooks, both in their fourth editions, and was the founding Editor-in-Chief of *Advances in Renal Replacement Therapy*, an official journal of the NKF. He currently is Editor-in-Chief of *Hemodialysis International*, the official journal of the International Society for Hemodialysis. He has more than 340 publications in the field of nephrology, dialysis, anemia management, and health care delivery and policy. Among his numerous honors is the President's Award of the NKF. He delivers more than 25 invited lectures each year and developed and chairs an annual second-year nephrology fellows preceptorship program, serving more than 65 Fellows from throughout the United States. Dr Nissenson has received research funds, grants or contracts from Amgen, Ortho Biotech, Roche, Watson and ARL.

**Gregorio T. Obrador, MD, MPH,** is Professor of Medicine and Dean at the Universidad Panamericana School of Medicine in Mexico City. He also serves as Adjunct Staff at the Division of Nephrology of the Tufts–New England Medical Center and Assistant Professor of Medicine at the Tufts University School of Medicine in Boston. While doing a clinical research fellowship at the Tufts–New England Medical Center and a Master of Public Health at Harvard University, he began a line of investigation in the area of CKD. Through several publications, he and others showed that the pre–ESRD management of patients with CKD is suboptimal, and that this is an important factor for the high morbidity and mortality observed in these patients. A particular area of interest has been anemia management before the initiation of dialysis therapy. By using population registry data, he and his colleagues have reported trends in anemia and iron management. Dr Obrador has served as reviewer for several journals, including *Kidney International*, the *Journal of the American Society of Nephrology*, and the *American Journal of Kidney Diseases*. He also has been a member of the Advisory Board of the NKF-KDOQI. Dr Obrador has received research funds, grants or contracts from Amgen, and is associated with the TREAT study.

**John C. Stivelman, MD,** is Chief Medical Officer of the Northwest Kidney Centers and Associate Professor of Medicine in the Division of Nephrology, Department of Medicine, at the University of Washington School of Medicine in Seattle. Dr Stivelman obtained his MD degree from the University of Pennsylvania, completed his residency in Internal Medicine at Harbor-UCLA Medical Center, and nephrology training at Brigham and Women's Hospital. Dr Stivelman has been involved in investigative efforts to optimize hematopoietic therapy for dialysis patients since the phase III recombinant erythropoietin trials in 1986. His major interests and literature contributions center on iron utilization,

mechanisms of resistance of erythropoietin therapy, improved dialytic survival in disadvantaged populations, and the interaction of regulatory issues with optimization of care. Dr Stivelman has served as the Chair of the Network 6 Medical Review Board and a member of the Forum of ESRD Networks Board of Directors. He currently serves as medical director of one of Northwest Kidney Centers' free-standing facilities and as a member of the Boards of Directors of the Renal Physicians' Association and the Northwest Renal Network (Network 16). Dr Stivelman has received research funds, grants or contracts from Watson, Amgen and Shire.

**David B. Van Wyck, MD** (*Work Group Co-Chair)*, is Professor of Medicine and Surgery at the University of Arizona College of Medicine in Tucson. After completing his undergraduate studies at Washington University, St Louis, Dr Van Wyck earned his MD at the University of Arizona College of Medicine. There, he undertook a research fellowship in Surgical Biology and completed his residency in Internal Medicine and fellowship in Nephrology. Dr Van Wyck has written or contributed to books, book chapters, articles, and abstracts on basic iron metabolism and reticuloendothelial function and on clinical aspects of iron and anemia in patients with CKD. On the subject of anemia and kidney disease, he pursues research, provides consultation to industry including American Regent, Amgen, and Gambro Healthcare, and reviews manuscripts for the major nephrology journals. Dr Van Wyck served on the original KDOQI Anemia Work Group. He assumed Chair responsibilities in 2002. Frequently invited to speak, Dr Van Wyck has lectured on the molecular and cellular control of erythropoiesis and iron homeostasis, diagnostic and treatment issues in anemia and iron management, protocol development in the treatment of dialysis-associated anemia, and new approaches to iron and erythropoietin replacement therapy. Dr Van Wyck has received research funds, grants or contracts from Amgen Inc., American Regent Inc., Gambro Healthcare and Shire Pharmaceuticals.

**Colin T. White, MD,** is a pediatric nephrologist at BC Children's Hospital in Vancouver and clinical assistant professor at the University of British Columbia in Canada. He completed medical school in Ottawa and Pediatrics in London, Ontario. There, he did 3 years of pediatric nephrology training before moving to Vancouver to complete 3 more years. He has been on staff as a Pediatric Nephrologist since 2003 and currently is the Director of Dialysis at BC Children's Hospital. He has a number of research interests, including medical education, optimizing dialysis care in children, estimation of GFR, and CKD and its complications. Dr White's interest in anemia management is geared toward children. He is presently completing a Masters degree in Medical Education. Dr White is associated with the CKid study and various NAPRTC protocols.

# ACKNOWLEDGMENTS

The Work Group appreciates the careful review of the draft guidelines and suggestions for improvement by external reviewers. Each comment was carefully considered and, whenever possible, suggestions for change were incorporated into the final report. As a result, the KDOQI Anemia in Chronic Kidney Disease guidelines is the product of the Work Group, the Evidence Review Team, the NKF, and all those who contributed their effort to improve the Guidelines.

The following individuals provided written review of the draft guidelines: Nihal Younis Abosaif, MD, Harith Aljebory, MD, Beth Ann Avanzado, BSN, RN, CNN, George R. Bailie, PharmD, PhD, Beth Bandor McCarthy, RN, Vinod K. Bansal, MD, Sally Burrows-Hudson, MS, RN, Carlos A. Caramelo, Dennis Cotter, MSE, Daniel W. Coyne, MD, Robert E. Cronin, Veta Cumbaa, RN, BA, CCA, Mike Cunningham, Neval Duman, MD, Earl J. Dunnigan, MD, FACP, Briggett C. Ford, Cheryl Gilmartin, PharmD, Marc Giovannini, Takanobu Imada, Atul V. Ingale, MD, Mark Kasselik, MD, Pam Kimball, MD, Janice Knouff, RN, BS, Chn, Craig B. Langman, MD, David J. Leehey, MD, Nathan W. Levin, MD, FACP, Yao-Lung Liu, MD, Francesco Locatelli, MD, Gerard M. London, MD, Victor Lorenzo, MD, Samir G. Mallat, MD, FASN, Donna Mapes, DNSc, MS, Luz Maria Munoz, Aletha Matsis, BSN, RN, CNN, Seiichi Matsuo, MD, Marva M. Moxey-Mims, MD, Andrew S. Narva, MD, Suzanne Norby, MD, Nancy J. Pelfrey, MSN, NP, Allen G. Peplinski, Suanna Petroff, Luana Pillon, MD, Francesco Pizzarelli, MD, Karthik Ranganna, MD, Pawan Rao, MD, Anton C. Schoolwerth, MD, FAHA, Douglas Schram, MD, Stephen Seliger, MD, Surendralal Shah, MD, Amita Sharma, MD, Bhupinder Singh, MD, Leah Smith, Stephanie J. Stewart, MSW, Rachel L. Sturdivant, MD, David Tovbin, MD, Edgar V. Lerma, MD, FACP, FASN, Lynne S. Weiss, Cheryl Weller, LCSW, Nanette Wenger, MD, Joseph W. Eschbach, MD, David C. Wheeler, MD, FRCP, Holly Whitcombe, MBA, CFRE, Yu Yang, Karen Yeates, MD, MPH.

Participation in the review does not necessarily constitute endorsement of the content of the report by the individuals or the organization or institution they represent.

The National Kidney Foundation, as well as the Work Group, would like to recognize the support of Amgen for the development of the Guidelines. The National Kidney Foundation is proud to partner with Amgen on this important initiative.

# REFERENCES


1. National Kidney Foundation: DOQI Clinical Practice Guidelines for the Treatment of Anemia of Chronic Renal Failure. Am J Kidney Dis 30:S192-S240, 1997 (suppl 3)

2. National Kidney Foundation: K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease: Update 2000. Am J Kidney Dis 37:S182-S238, 2001 (suppl 1)

3. National Kidney Foundation: K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. Am J Kidney Dis 43:S1-S290, 2004 (suppl 1)

4. National Kidney Foundation: K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, classification, and stratification. Am J Kidney Dis 39:S1-S266, 2002 (suppl 1)

5. US Renal Data System: USRDS 2000 Annual Data Report. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2000

6. National Kidney Foundation: K/DOQI Clinical Practice Guidelines for Management of Dyslipidemias in Patients With Kidney Disease. Am J Kidney Dis 41:S1-S91, 2003 (suppl 3)

7. National Kidney Foundation: K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. Am J Kidney Dis 42:S1-S201, 2003 (suppl 3)

8. National Kidney Foundation: K/DOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure. Am J Kidney Dis 35:S1-S140, 2000 (suppl 1)

9. National Kidney Foundation: K/DOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients. Am J Kidney Dis 45:S1-S153, 2005 (suppl 3)

10. Gilbertson DT, Liu J, Xue JL, et al: Projecting the number of patients with end-stage renal disease in the United States to the year 2015. J Am Soc Nephrol 16:3736-3741, 2005

11. Donnelly S: Why is erythropoietin made in the kidney? The kidney functions as a critmeter. Am J Kidney Dis 38:415-425, 2001

12. Metzen E, Ratcliffe PJ: HIF hydroxylation and cellular oxygen sensing. Biol Chem 385:223-230, 2004

13. Koury MJ, Ponka P: New insights into erythropoiesis: The roles of folate, vitamin $B_{12}$, and iron. Annu Rev Nutr 24:105-131, 2004

14. De Maria R, Testa U, Luchetti L, et al: Apoptotic role of Fas/Fas ligand system in the regulation of erythropoiesis. Blood 93:796-803, 1999

15. Andrews NC: Anemia of inflammation: The cytokine-hepcidin link. J Clin Invest 113:1251-1253, 2004

16. Locatelli F, Aljama P, Barany P, et al: Revised European Best Practice Guidelines for the management of anaemia in patients with chronic renal failure. Nephrol Dial Transplant 19:Sii1-Sii47, 2004 (suppl 2)

17. Eschbach JW, Adamson JW: Anemia of end-stage renal disease (ESRD). Kidney Int 28:1-5, 1985

18. Radtke HW, Claussner A, Erbes PM, Scheuermann EH, Schoeppe W, Koch KM: Serum erythropoietin concentration in chronic renal failure: Relationship to degree of anemia and excretory renal function. Blood 54:877-884, 1979

19. McGonigle RJ, Wallin JD, Shadduck RK, Fisher JW: Erythropoietin deficiency and inhibition of erythropoiesis in renal insufficiency. Kidney Int 25:437-444, 1984

20. Fisher JW: Mechanism of the anemia of chronic renal failure. Nephron 25:106-111, 1980

21. Erslev AJ, Besarab A: The rate and control of baseline red cell production in hematologically stable patients with uremia. J Lab Clin Med 126:283-286, 1995

22. Besarab A, Levin A: Defining a renal anemia management period. Am J Kidney Dis 36:S13-S23, 2000. (suppl 1)

23. Chandra M, Miller ME, Garcia JF, Mossey RT, McVicar M: Serum immunoreactive erythropoietin levels in patients with polycystic kidney disease as compared with other hemodialysis patients. Nephron 39:26-29, 1985

24. Eschbach JW Jr, Funk D, Adamson J, Kuhn I, Scribner BH, Finch CA: Erythropoiesis in patients with renal failure undergoing chronic dialysis. N Engl J Med 276:653-658, 1967

25. Hsu CY, Bates DW, Kuperman GJ, Curhan GC: Relationship between hematocrit and renal function in men and women. Kidney Int 59:725-731, 2001

26. Hsu CY, McCulloch CE, Curhan GC: Epidemiology of anemia associated with chronic renal insufficiency among adults in the United States: Results from the Third National Health and Nutrition Examination Survey. J Am Soc Nephrol 13:504-510, 2002

27. Astor BC, Muntner P, Levin A, Eustace JA, Coresh J: Association of kidney function with anemia: The Third National Health and Nutrition Examination Survey (1988-1994). Arch Intern Med 162:1401-1408, 2002

28. US Renal Data System: USRDS 2004 Annual Data Report. Bethesda, MD, The National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2004

29. McClellan W, Aronoff SL, Bolton WK, et al: The prevalence of anemia in patients with chronic kidney disease. Curr Med Res Opin 20:1501-1510, 2004

30. Levin A, Thompson CR, Ethier J, et al: Left ventricular mass index increase in early renal disease: Impact of decline in hemoglobin. Am J Kidney Dis 34:125-134, 1999

31. Obrador GT, Ruthazer R, Arora P, Kausz AT, Pereira BJ: Prevalence of and factors associated with suboptimal care before initiation of dialysis in the United States. J Am Soc Nephrol 10:1793-1800, 1999

32. Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC: Prevalence of anemia in persons 65 years and older in the United States: Evidence for a high rate of unexplained anemia. Blood 104:2263-2268, 2004

33. Ishimura E, Nishizawa Y, Okuno S, et al: Diabetes mellitus increases the severity of anemia in non-dialyzed patients with renal failure. J Nephrol 11:83-86, 1998

34. Bosman DR, Winkler AS, Marsden JT, Macdougall IC, Watkins PJ: Anemia with erythropoietin deficiency occurs early in diabetic nephropathy. Diabetes Care 24:495-499, 2001

35. Thomas MC, MacIsaac RJ, Tsalamandris C, Power D, Jerums G: Unrecognized anemia in patients with diabetes: A cross-sectional survey. Diabetes Care 26:1164-1169, 2003

36. Thomas MC, MacIsaac RJ, Tsalamandris C, et al: The burden of anaemia in type 2 diabetes and the role of nephropathy: A cross-sectional audit. Nephrol Dial Transplant 19:1792-1797, 2004

37. El-Achkar TM, Ohmit SE, McCullough PA, et al: Higher prevalence of anemia with diabetes mellitus in moderate kidney insufficiency: The Kidney Early Evaluation Program. Kidney Int 67:1483-1488, 2005

38. Roger SD, McMahon LP, Clarkson A, et al: Effects of early and late intervention with epoetin alpha on left ventricular mass among patients with chronic kidney disease (stage 3 or 4): Results of a randomized clinical trial. J Am Soc Nephrol 15:148-156, 2004

39. Levin A, Djurdjev O, Thompson C, et al: Canadian randomized trial of hemoglobin maintenance to prevent or delay left ventricular mass growth in patients with CKD. Am J Kidney Dis 46:799-811, 2005

40. Hollowell JG, van Assendelft OW, Gunter EW, Lewis BG, Najjar M, Pfeiffer C: Hematological and iron-related analytes—Reference data for persons aged 1 year and over: United States, 1988-94. Vital Health Stat 11:1-156, 2005

41. Centers for Disease Control and Prevention: Recommendations to prevent and control iron deficiency in the United States. MMWR Recomm Rep 47:1-29, 1998

42. World Health Organization: Iron Deficiency Anaemia: Assessment, Prevention and Control. A Guide for Programme Managers. Geneva, Switzerland, World Health Organization, 2001

43. Levin A: How should anaemia be managed in pre-dialysis patients? Nephrol Dial Transplant 14:S66-S74, 1999 (suppl 2)

44. Xue JL, St Peter WL, Ebben JP, Everson SE, Collins AJ: Anemia treatment in the pre-ESRD period and associated mortality in elderly patients. Am J Kidney Dis 40:1153-1161, 2002

45. Parfrey PS, Foley RN, Harnett JD, Kent GM, Murray DC, Barre PE: Outcome and risk factors for left ventricular disorders in chronic uraemia. Nephrol Dial Transplant 11:1277-1285, 1996

46. Levin A, Foley RN: Cardiovascular disease in chronic renal insufficiency. Am J Kidney Dis 36:S24-S30, 2000 (suppl 1)

47. Kausz AT, Obrador GT, Pereira BJ: Anemia management in patients with chronic renal insufficiency. Am J Kidney Dis 36:S39-S51, 2000 (suppl 1)

48. Locatelli F, Conte F, Marcelli D: The impact of haematocrit levels and erythropoietin treatment on overall and cardiovascular mortality and morbidity—The experience of the Lombardy Dialysis Registry. Nephrol Dial Transplant 13:1642-1644, 1998

49. Canadian Erythropoietin Study Group: Association between recombinant human erythropoietin and quality of life and exercise capacity of patients receiving haemodialysis. BMJ 300:573-578, 1990

50. Ritz E, Eisenhardt A: Early epoetin treatment in patients with renal insufficiency. Nephrol Dial Transplant 15:S40-S44, 2000 (suppl 3)

51. Pugh LG: Muscular exercise on Mount Everest. J Physiol 141:233-261, 1958

52. Beall CM, Goldstein MC: Hemoglobin concentration of pastoral nomads permanently resident at 4,850-5,450 meters in Tibet. Am J Phys Anthropol 73:433-438, 1987

53. Richalet JP, Souberbielle JC, Antezana AM, et al: Control of erythropoiesis in humans during prolonged exposure to the altitude of 6,542 m. Am J Physiol 266:R756-R764, 1994

54. Whitehead TP, Robinson D, Hale AC, Bailey AR: Clinical chemistry and haematology: Adult reference values. London, UK, BUPA Medical Research, 1994

55. National Kidney Foundation: Kidney Early Evaluation Program. Am J Kidney Dis 45:S1-S135, 2005 (suppl 2)

56. Berkahn L, Keating A: Hematopoiesis in the elderly. Hematology 9:159-163, 2004

57. Svanberg B, Arvidsson B, Norrby A, Rybo G, Solvell L: Absorption of supplemental iron during pregnancy—A longitudinal study with repeated bone-marrow studies and absorption measurements. Acta Obstet Gynecol Scand Suppl 48:S87-S108, 1975

58. Puolakka J, Janne O, Pakarinen A, Jarvinen PA, Vihko R: Serum ferritin as a measure of iron stores during and after normal pregnancy with and without iron supplements. Acta Obstet Gynecol Scand Suppl 95:S43-S51, 1980

59. Taylor DJ, Mallen C, McDougall N, Lind T: Effect of iron supplementation on serum ferritin levels during and after pregnancy. Br J Obstet Gynaecol 89:1011-1017, 1982

60. Meyers LD, Habicht JP, Johnson CL: Components of the difference in hemoglobin concentrations in blood between black and white women in the United States. Am J Epidemiol 109:539-549, 1979

61. Cresanta JL, Croft JB, Webber LS, Nicklas TA, Berenson GS: Racial difference in hemoglobin concentration of young adults. Prev Med 16:659-669, 1987

62. Pan WH, Habicht JP: The non-iron-deficiency-related difference in hemoglobin concentration distribution between blacks and whites and between men and women. Am J Epidemiol 134:1410-1416, 1991

63. Jackson RT: Separate hemoglobin standards for blacks and whites: A critical review of the case for separate and unequal hemoglobin standards. Med Hypotheses 32:181-189, 1990

64. Johnson-Spear MA, Yip R: Hemoglobin difference between black and white women with comparable iron status: Justification for race-specific anemia criteria. Am J Clin Nutr 60:117-121, 1994

65. Tirlapur VG, Gicheru K, Charalambous BM, Evans PJ, Mir MA: Packed cell volume, haemoglobin, and oxygen saturation changes in healthy smokers and non-smokers. Thorax 38:785-787, 1983

66. Taralov Z, Koumtchev E, Lyutakova Z: Erythrocyte ferritin levels in chronic renal failure patients. Folia Med (Plovdiv) 40:65-70, 1998

67. Clyne N, Jogestrand T, Lins LE, Pehrsson SK: Progressive decline in renal function induces a gradual decrease in total hemoglobin and exercise capacity. Nephron 67:322-326, 1994

68. Nankivell BJ, Allen RD, O'Connell PJ, Chapman JR: Erythrocytosis after renal transplantation: Risk factors and relationship with GFR. Clin Transplant 9:375-382, 1995

69. de Klerk G, Wilmink JM, Rosengarten PC, Vet RJ, Goudsmit R: Serum erythropoietin (ESF) titers in anemia of chronic renal failure. J Lab Clin Med 100:720-734, 1982

70. Urabe A, Saito T, Fukamachi H, Kubota M, Takaku F: Serum erythropoietin titers in the anemia of chronic renal failure and other hematological states. Int J Cell Cloning 5:202-208, 1987

71. Silverberg DS, Iaina A, Peer G, et al: Intravenous iron supplementation for the treatment of the anemia of moderate to severe chronic renal failure patients not receiving dialysis. Am J Kidney Dis 27:234-238, 1996

72. Lin JL, Kou MT, Leu ML: Effect of long-term low-dose aluminum-containing agents on hemoglobin synthesis in patients with chronic renal insufficiency. Nephron 74:33-38, 1996

73. Clyne N, Jogestrand T: Effect of erythropoietin treatment on physical exercise capacity and on renal function in predialytic uremic patients. Nephron 60:390-396, 1992

74. Portoles J, Torralbo A, Martin P, Rodrigo J, Herrero JA, Barrientos A: Cardiovascular effects of recombinant human erythropoietin in predialysis patients. Am J Kidney Dis 29:541-548, 1997

75. Dimitrakov D, Kumchev E, Tllkian E: Study of the effect of recombinant erythropoietin on renal anaemia in predialysis patients with chronic renal failure. Folia Med (Plovdiv) 36:31-36, 1994

76. Klahr S, Breyer JA, Beck GJ, et al: Dietary protein restriction, blood pressure control, and the progression of polycystic kidney disease. Modification of Diet in Renal Disease Study Group. J Am Soc Nephrol 5:2037-2047, 1995

77. Howard AD, Moore J Jr, Welch PG, Gouge SF: Analysis of the quantitative relationship between anemia and chronic renal failure. Am J Med Sci 297:309-313, 1989

78. Lim VS, Fangman J, Flanigan MJ, DeGowin RL, Abels RT: Effect of recombinant human erythropoietin on renal function in humans. Kidney Int 37:131-136, 1990

79. Besarab A, Caro J, Jarrell B, et al: Effect of cyclosporine and delayed graft function on posttransplantation erythropoiesis. Transplantation 40:624-631, 1985

80. Brod J, Hornych A: Effect of correction of anemia on the glomerular filtration rate in chronic renal failure. Isr J Med Sci 3:53-59, 1967

81. Roth D, Smith RD, Schulman G, et al: Effects of recombinant human erythropoietin on renal function in chronic renal failure predialysis patients. Am J Kidney Dis 24:777-784, 1994

82. Kuriyama S, Tomonari H, Yoshida H, Hashimoto T, Kawaguchi Y, Sakai O: Reversal of anemia by erythropoietin therapy retards the progression of chronic renal failure, especially in nondiabetic patients. Nephron 77:176-185, 1997

83. Hayashi T, Suzuki A, Shoji T, et al: Cardiovascular effect of normalizing the hematocrit level during erythropoietin therapy in predialysis patients with chronic renal failure. Am J Kidney Dis 35:250-256, 2000

84. Schwartz AB, Prior JE, Mintz GS, Kim KE, Kahn SB: Cardiovascular hemodynamic effects of correction of anemia of chronic renal failure with recombinant-human erythropoietin. Transplant Proc 23:1827-1830, 1991

85. Fehr T, Ammann P, Garzoni D, et al: Interpretation of erythropoietin levels in patients with various degrees of renal insufficiency and anemia. Kidney Int 66:1206-1211, 2004

86. Morris MW, Davey FR: Basic examination of blood, in Henry JB (ed): Clinical Diagnosis and Management by Laboratory Methods. Philadelphia, PA, WB Saunders, 1996, pp 549-593

87. Brittin GM, Brecher G, Johnson CA, Elashoff RM: Stability of blood in commonly used anticoagulants. Use of refrigerated blood for quality control of the Coulter Counter Model S. Am J Clin Pathol 52:690-694, 1969

88. Holt JT, DeWandler MJ, Arvan DA: Spurious elevation of the electronically determined mean corpuscular volume and hematocrit caused by hyperglycemia. Am J Clin Pathol 77:561-567, 1982

89. van Duijnhoven HL, Treskes M: Marked interference of hyperglycemia in measurements of mean (red) cell volume by Technicon H analyzers. Clin Chem 42:76-80, 1996

90. Paterakis GS, Laoutaris NP, Alexia SV, et al: The effect of red cell shape on the measurement of red cell volume. A proposed method for the comparative assessment of this effect among various haematology analysers. Clin Lab Haematol 16:235-245, 1994

91. Fraser CG, Wilkinson SP, Neville RG, Knox JD, King JF, MacWalter RS: Biologic variation of common hematologic laboratory quantities in the elderly. Am J Clin Pathol 92:465-470, 1989

92. Movilli E, Pertica N, Camerini C, et al: Predialysis versus postdialysis hematocrit evaluation during erythropoietin therapy. Am J Kidney Dis 39:850-853, 2002

93. Bellizzi V, Minutolo R, Terracciano V, et al: Influence of the cyclic variation of hydration status on hemoglobin levels in hemodialysis patients. Am J Kidney Dis 40:549-555, 2002

94. Hillman RS, Finch CA: Red Cell Manual (ed 7). Philadelphia, PA, Davis, 1996

95. Naets JP, Garcia JF, Tousaaint C, Buset M, Waks D: Radioimmunoassay of erythropoietin in chronic uraemia or anephric patients. Scand J Haematol 37:390-394, 1986

96. Ross RP, McCrea JB, Besarab A: Erythropoietin response to blood loss in hemodialysis patients in blunted but preserved. ASAIO J 40:M880-M885, 1994

97. Fishbane S, Lynn RI: The efficacy of iron dextran for the treatment of iron deficiency in hemodialysis patients. Clin Nephrol 44:238-240, 1995

98. Fernandez-Rodriguez AM, Guindeo-Casasus MC, Molero-Labarta T, et al: Diagnosis of iron deficiency in chronic renal failure. Am J Kidney Dis 34:508-513, 1999

99. Kalantar-Zadeh K, Hoffken B, Wunsch H, Fink H, Kleiner M, Luft FC: Diagnosis of iron deficiency anemia in renal failure patients during the post-erythropoietin era. Am J Kidney Dis 26:292-299, 1995

100. Annibale B, Lahner E, Chistolini A, et al: Endoscopic evaluation of the upper gastrointestinal tract is worthwhile in premenopausal women with iron-deficiency anaemia irrespective of menstrual flow. Scand J Gastroenterol 38:239-245, 2003

101. Coban E, Timuragaoglu A, Meric M: Iron deficiency anemia in the elderly: Prevalence and endoscopic evaluation

of the gastrointestinal tract in outpatients. Acta Haematol 110:25-28, 2003

102. Ioannou GN, Rockey DC, Bryson CL, Weiss NS: Iron deficiency and gastrointestinal malignancy: A population-based cohort study. Am J Med 113:276-280, 2002

103. Ioannou GN, Spector J, Scott K, Rockey DC: Prospective evaluation of a clinical guideline for the diagnosis and management of iron deficiency anemia. Am J Med 113:281-287, 2002

104. Goddard AF, McIntyre AS, Scott BB: Guidelines for the management of iron deficiency anaemia. British Society of Gastroenterology. Gut 46:SIV1-SIV5, 2000 (suppl 3-4)

105. Joosten E, Ghesquiere B, Linthoudt H, et al: Upper and lower gastrointestinal evaluation of elderly inpatients who are iron deficient. Am J Med 107:24-29, 1999

106. Ho CH, Chau WK, Hsu HC, Gau JP, You JY, Chen CC: Predictive risk factors and prevalence of malignancy in patients with iron deficiency anemia in Taiwan. Am J Hematol 78:108-112, 2005

107. Akmal M, Sawelson S, Karubian F, Gadallah M: The prevalence and significance of occult blood loss in patients with predialysis advanced chronic renal failure (CRF), or receiving dialytic therapy. Clin Nephrol 42:198-202, 1994

108. Besarab A, Bolton WK, Browne JK, et al: The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med 339:584-590, 1998

109. Parfrey PS, Foley RN, Wittreich BH, Sullivan DJ, Zagari MJ, Frei D: Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. J Am Soc Nephrol 16:2180-2189, 2005

110. Foley RN, Parfrey PS, Morgan J, et al: Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. Kidney Int 58:1325-1335, 2000

111. Lacson E Jr, Ofsthun N, Lazarus JM: Effect of variability in anemia management on hemoglobin outcomes in ESRD. Am J Kidney Dis 41:111-124, 2003

112. Collins AJ, Brenner RM, Ofman JJ, et al: Epoetin alfa use in patients with ESRD: An analysis of recent US prescribing patterns and hemoglobin outcomes. Am J Kidney Dis 46:481-488, 2005

113. Berns JS, Elzein H, Lynn RI, Fishbane S, Meisels IS, Deoreo PB: Hemoglobin variability in epoetin-treated hemodialysis patients. Kidney Int 64:1514-1521, 2003

114. Fishbane S, Berns JS: Hemoglobin cycling in hemodialysis patients treated with recombinant human erythropoietin. Kidney Int 68:1337-1343, 2005

115. Eckardt KU: The CREATE trial—Building the evidence. Nephrol Dial Transplant 16:S16-S18, 2001 (suppl 2)

115A. US National Institutes of Health: CHOIR Trial. 2005. Available at: www.clinicaltrials.gov/ct/show/NCT00211120?order=1. Accessed March 31, 2006

116. Man-Son-Hing M, Gage BF, Montgomery AA, et al: Preference-based antithrombotic therapy in atrial fibrillation: Implications for clinical decision making. Med Decis Making 25:548-559, 2005

117. Canadian Erythropoietin Study Group: Effect of recombinant human erythropoietin therapy on blood pressure in hemodialysis patients. Am J Nephrol 11:23-26, 1991

118. Furuland H, Linde T, Ahlmen J, Christensson A, Strombom U, Danielson BG: A randomized controlled trial of haemoglobin normalization with epoetin alfa in predialysis and dialysis patients. Nephrol Dial Transplant 18:353-361, 2003

119. Suzuki M, Hirasawa Y, Hirashima K, et al: Dose-finding, double-blind, clinical trial of recombinant human erythropoietin (Chugai) in Japanese patients with end-stage renal disease. Research Group for Clinical Assessment of rhEPO. Contrib Nephrol 76:179-192; discussion 212-178, 1989

120. Furuland H, Linde T, Wikstrom B, Danielson BG: Reduced hemodialysis adequacy after hemoglobin normalization with epoetin. J Nephrol 18:80-85, 2005

121. McMahon LP, Mason K, Skinner SL, Burge CM, Grigg LE, Becker GJ: Effects of haemoglobin normalization on quality of life and cardiovascular parameters in end-stage renal failure. Nephrol Dial Transplant 15:1425-1430, 2000

122. McMahon LP, McKenna MJ, Sangkabutra T, et al: Physical performance and associated electrolyte changes after haemoglobin normalization: A comparative study in haemodialysis patients. Nephrol Dial Transplant 14:1182-1187, 1999

123. Nissenson AR, Korbet S, Faber M, et al: Multicenter trial of erythropoietin in patients on peritoneal dialysis. J Am Soc Nephrol 5:1517-1529, 1995

124. Bahlmann J, Schoter KH, Scigalla P, et al: Morbidity and mortality in hemodialysis patients with and without erythropoietin treatment: A controlled study. Contrib Nephrol 88:90-106, 1991

125. Sikole A, Polenakovic M, Spirovska V, Polenakovic B, Masin G: Analysis of heart morphology and function following erythropoietin treatment of anemic dialysis patients. Artif Organs 17:977-984, 1993

126. Morris KP, Sharp J, Watson S, Coulthard MG: Non-cardiac benefits of human recombinant erythropoietin in end stage renal failure and anaemia. Arch Dis Child 69:580-586, 1993

127. Abraham PA, Macres MG: Blood pressure in hemodialysis patients during amelioration of anemia with erythropoietin. J Am Soc Nephrol 2:927-936, 1991

128. Berns JS, Rudnick MR, Cohen RM, Bower JD, Wood BC: Effects of normal hematocrit on ambulatory blood pressure in epoetin-treated hemodialysis patients with cardiac disease. Kidney Int 56:253-260, 1999

129. Conlon PJ, Kovalik E, Schumm D, Minda S, Schwab SJ: Normalization of hematocrit in hemodialysis patients with cardiac disease does not increase blood pressure. Ren Fail 22:435-444, 2000

130. Levin A: The relationship of haemoglobin level and survival: Direct or indirect effects? Nephrol Dial Transplant 17:S8-S13, 2002 (suppl 5)

130A. Levin A, Djurdjev O, Thompson C, et al: Canadian randomized trial of hemoglobin maintenance to prevent or delay left ventricular mass growth in patients with CKD. Am J Kidney Dis 46:799-811, 2005

131. Lim VS, DeGowin RL, Zavala D, et al: Recombinant human erythropoietin treatment in pre-dialysis patients. A double-blind placebo-controlled trial. Ann Intern Med 110: 108-114, 1989

132. Revicki DA, Brown RE, Feeny DH, et al: Health-related quality of life associated with recombinant human erythropoietin therapy for predialysis chronic renal disease patients. Am J Kidney Dis 25:548-554, 1995

133. Kleinman KS, Schweitzer SU, Perdue ST, Bleifer KH, Abels RI: The use of recombinant human erythropoietin in the correction of anemia in predialysis patients and its effect on renal function: A double-blind, placebo-controlled trial. Am J Kidney Dis 14:486-495, 1989

134. Watson AJ, Gimenez LF, Cotton S, Walser M, Spivak JL: Treatment of the anemia of chronic renal failure with subcutaneous recombinant human erythropoietin. Am J Med 89:432-435, 1990

135. Abraham PA, Opsahl JA, Rachael KM, Asinger R, Halstenson CE: Renal function during erythropoietin therapy for anemia in predialysis chronic renal failure patients. Am J Nephrol 10:128-136, 1990

136. Locatelli F, Baldamus CA, Villa G, Ganea A, Martin de Francisco AL: Once-weekly compared with three-times-weekly subcutaneous epoetin beta: Results from a randomized, multicenter, therapeutic-equivalence study. Am J Kidney Dis 40:119-125, 2002

137. Locatelli F, Canaud B, Giacardy F, Martin-Malo A, Baker N, Wilson J: Treatment of anaemia in dialysis patients with unit dosing of darbepoetin alfa at a reduced dose frequency relative to recombinant human erythropoietin (rHuEpo). Nephrol Dial Transplant 18:362-369, 2003

138. Nissenson AR, Swan SK, Lindberg JS, et al: Randomized, controlled trial of darbepoetin alfa for the treatment of anemia in hemodialysis patients. Am J Kidney Dis 40:110-118, 2002

139. Tolman C, Richardson D, Bartlett C, Will E: Structured conversion from thrice weekly to weekly erythropoietic regimens using a computerized decision-support system: A randomized clinical study. J Am Soc Nephrol 16:1463-1470, 2005

140. Kaufman JS, Reda DJ, Fye CL, et al: Subcutaneous compared with intravenous epoetin in patients receiving hemodialysis. Department of Veterans Affairs Cooperative Study Group on Erythropoietin in Hemodialysis Patients. N Engl J Med 339:578-583, 1998

141. Vanrenterghem Y, Barany P, Mann JF, et al: Randomized trial of darbepoetin alfa for treatment of renal anemia at a reduced dose frequency compared with rHuEPO in dialysis patients. Kidney Int 62:2167-2175, 2002

142. Ling B, Walczyk M, Agarwal A, Carroll W, Liu W, Brenner R: Darbepoetin alfa administered once monthly maintains hemoglobin concentrations in patients with chronic kidney disease. Clin Nephrol 63:327-334, 2005

143. Jadoul M, Vanrenterghem Y, Foret M, Walker R, Gray SJ: Darbepoetin alfa administered once monthly maintains haemoglobin levels in stable dialysis patients. Nephrol Dial Transplant 19:898-903, 2004

144. Eschbach JW, Abdulhadi MH, Browne JK, et al: Recombinant human erythropoietin in anemic patients with end-stage renal disease. Results of a phase III multicenter clinical trial. Ann Intern Med 111:992-1000, 1989

145. Eschbach JW, Kelly MR, Haley NR, Abels RI, Adamson JW: Treatment of the anemia of progressive renal failure with recombinant human erythropoietin. N Engl J Med 321:158-163, 1989

146. Locatelli F, Olivares J, Walker R, et al: Novel erythropoiesis stimulating protein for treatment of anemia in chronic renal insufficiency. Kidney Int 60:741-747, 2001

147. Toto RD, Pichette V, Navarro J, et al: Darbepoetin alfa effectively treats anemia in patients with chronic kidney disease with de novo every-other-week administration. Am J Nephrol 24:453-460, 2004

148. Besarab A, Amin N, Ahsan M, et al: Optimization of epoetin therapy with intravenous iron therapy in hemodialysis patients. J Am Soc Nephrol 11:530-538, 2000

149. DeVita MV, Frumkin D, Mittal S, Kamran A, Fishbane S, Michelis MF: Targeting higher ferritin concentrations with intravenous iron dextran lowers erythropoietin requirement in hemodialysis patients. Clin Nephrol 60:335-340, 2003

150. Chang CH, Chang CC, Chiang SS: Reduction in erythropoietin doses by the use of chronic intravenous iron supplementation in iron-replete hemodialysis patients. Clin Nephrol 57:136-141, 2002

151. Fishbane S, Galgano C, Langley RC Jr, Canfield W, Maesaka JK: Reticulocyte hemoglobin content in the evaluation of iron status of hemodialysis patients. Kidney Int 52:217-222, 1997

152. Fishbane S, Kowalski EA, Imbriano LJ, Maesaka JK: The evaluation of iron status in hemodialysis patients. J Am Soc Nephrol 7:2654-2657, 1996

153. Chuang CL, Liu RS, Wei YH, Huang TP, Tarng DC: Early prediction of response to intravenous iron supplementation by reticulocyte haemoglobin content and high-fluorescence reticulocyte count in haemodialysis patients. Nephrol Dial Transplant 18:370-377, 2003

154. Tessitore N, Solero GP, Lippi G, et al: The role of iron status markers in predicting response to intravenous iron in haemodialysis patients on maintenance erythropoietin. Nephrol Dial Transplant 16:1416-1423, 2001

155. Mittman N, Sreedhara R, Mushnick R, et al: Reticulocyte hemoglobin content predicts functional iron deficiency in hemodialysis patients receiving rHuEPO. Am J Kidney Dis 30:912-922, 1997

156. Fishbane S, Frei GL, Maesaka J: Reduction in recombinant human erythropoietin doses by the use of chronic intravenous iron supplementation. Am J Kidney Dis 26:41-46, 1995

157. Fishbane S, Shapiro W, Dutka P, Valenzuela OF, Faubert J: A randomized trial of iron deficiency testing strategies in hemodialysis patients. Kidney Int 60:2406-2411, 2001

158. Kaneko Y, Miyazaki S, Hirasawa Y, Gejyo F, Suzuki M: Transferrin saturation versus reticulocyte hemoglobin content for iron deficiency in Japanese hemodialysis patients. Kidney Int 63:1086-1093, 2003

159. Mitsuiki K, Harada A, Miyata Y: Assessment of iron deficiency in chronic hemodialysis patients: Investigation of cutoff values for reticulocyte hemoglobin content. Clin Exp Nephrol 7:52-57, 2003

160. Besarab A, Kaiser JW, Frinak S: A study of parenteral iron regimens in hemodialysis patients. Am J Kidney Dis 34:21-28, 1999

161. Lin JL, Chang MY, Tan DT, Leu ML: Short-term small-dose intravenous iron trial to detect functional iron deficiency in dialysis patients. Am J Nephrol 21:91-97, 2001

162. Low CL, Bailie GR, Eisele G: Sensitivity and specificity of transferrin saturation and serum ferritin as markers of iron status after intravenous iron dextran in hemodialysis patients. Ren Fail 19:781-788, 1997

163. Canavese C, Bergamo D, Ciccone G, et al: Validation of serum ferritin values by magnetic susceptometry in predicting iron overload in dialysis patients. Kidney Int 65:1091-1098, 2004

164. Kalantar-Zadeh K, Regidor DL, McAllister CJ, Michael B, Warnock DG: Time-dependent associations between iron and mortality in hemodialysis patients. J Am Soc Nephrol 16:3070-3080, 2005

165. Feldman HI, Joffe M, Robinson B, Knauss J, et al: Administration of parenteral iron and mortality among hemodialysis patients. J Am Soc Nephrol 15:1623-1632, 2004

166. Macdougall IC, Tucker B, Thompson J, Tomson CR, Baker LR, Raine AE: A randomized controlled study of iron supplementation in patients treated with erythropoietin. Kidney Int 50:1694-1699, 1996

167. Fudin R, Jaichenko J, Shostak A, Bennett M, Gotloib L: Correction of uremic iron deficiency anemia in hemodialyzed patients: A prospective study. Nephron 79:299-305, 1998

168. Nissenson AR, Berns JS, Sakiewicz P, et al: Clinical evaluation of heme iron polypeptide: Sustaining a response to rHuEPO in hemodialysis patients. Am J Kidney Dis 42:325-330, 2003

169. Van Wyck DB, Roppolo M, Martinez CO, Mazey RM, McMurray S: A randomized, controlled trial comparing IV iron sucrose to oral iron in anemic patients with nondialysis-dependent CKD. Kidney Int 68:2846-2856, 2005

170. Aggarwal HK, Nand N, Singh S, Singh M, Hemant, Kaushik G: Comparison of oral versus intravenous iron therapy in predialysis patients of chronic renal failure receiving recombinant human erythropoietin. J Assoc Physicians India 51:170-174, 2003

171. Stoves J, Inglis H, Newstead CG: A randomized study of oral vs intravenous iron supplementation in patients with progressive renal insufficiency treated with erythropoietin. Nephrol Dial Transplant 16:967-974, 2001

172. Charytan C, Qunibi W, Bailie GR: Comparison of intravenous iron sucrose to oral iron in the treatment of anemic patients with chronic kidney disease not on dialysis. Nephron Clin Pract 100:c55-c62, 2005

173. Novey HS, Pahl M, Haydik I, Vaziri ND: Immunologic studies of anaphylaxis to iron dextran in patients on renal dialysis. Ann Allergy 72:224-228, 1994

174. Agarwal R, Vasavada N, Sachs NG, Chase S: Oxidative stress and renal injury with intravenous iron in patients with chronic kidney disease. Kidney Int 65:2279-2289, 2004

175. Michael B, Coyne DW, Fishbane S, et al: Sodium ferric gluconate complex in hemodialysis patients: Adverse reactions compared to placebo and iron dextran. Kidney Int 61:1830-1839, 2002

176. Walters BA, Van Wyck DB: Benchmarking iron dextran sensitivity: reactions requiring resuscitative medication in incident and prevalent patients. Nephrol Dial Transplant 20:1438-1442, 2005

177. Fletes R, Lazarus JM, Gage J, Chertow GM: Suspected iron dextran-related adverse drug events in hemodialysis patients. Am J Kidney Dis 37:743-749, 2001

178. Hamstra RD, Block MH, Schocket AL: Intravenous iron dextran in clinical medicine. JAMA 243:1726-1731, 1980

179. Fishbane S, Ungureanu VD, Maesaka JK, Kaupke CJ, Lim V, Wish J: The safety of intravenous iron dextran in hemodialysis patients. Am J Kidney Dis 28:529-534, 1996

180. Faich G, Strobos J: Sodium ferric gluconate complex in sucrose: Safer intravenous iron therapy than iron dextrans. Am J Kidney Dis 33:464-470, 1999

181. Bailie GR, Clark JA, Lane CE, Lane PL: Hypersensitivity reactions and deaths associated with intravenous iron preparations. Nephrol Dial Transplant 20:1443-1449, 2005

182. Stang PE, Fox JL: Adverse drug events and the Freedom of Information Act: An apple in Eden. Ann Pharmacother 26:238-243, 1992

183. Brimble KS, Rabbat CG, McKenna P, Lambert K, Carlisle EJ: Protocolized anemia management with erythropoietin in hemodialysis patients: A randomized controlled trial. J Am Soc Nephrol 14:2654-2661, 2003

184. Cervelli MJ, Gray N, McDonald S, Gentgall MG, Disney AP: Randomized cross-over comparison of intravenous and subcutaneous darbepoetin dosing efficiency in haemodialysis patients. Nephrology (Carlton) 10:129-135, 2005

185. Markowitz GS, Kahn GA, Feingold RE, Coco M, Lynn RI: An evaluation of the effectiveness of oral iron therapy in hemodialysis patients receiving recombinant human erythropoietin. Clin Nephrol 48:34-40, 1997

186. McCarthy JT, Regnier CE, Loebertmann CL, Bergstralh EJ: Adverse events in chronic hemodialysis patients receiving intravenous iron dextran—A comparison of two products. Am J Nephrol 20:455-462, 2000

187. Aronoff GR, Bennett WM, Blumenthal S, et al: Iron sucrose in hemodialysis patients: Safety of replacement and maintenance regimens. Kidney Int 66:1193-1198, 2004

188. Blaustein DA, Schwenk MH, Chattopadhyay J, et al: The safety and efficacy of an accelerated iron sucrose dosing regimen in patients with chronic kidney disease. Kidney Int Suppl 64:S72-S77, 2003

189. Charytan C, Schwenk MH, Al-Saloum MM, Spinowitz BS: Safety of iron sucrose in hemodialysis patients intolerant to other parenteral iron products. Nephron Clin Pract 96:c63-c66, 2004

190. Aronoff GR: Safety of intravenous iron in clinical practice: Implications for anemia management protocols. J Am Soc Nephrol 15:S99-S106, 2004 (suppl 2)

191. Hoppel C: The role of carnitine in normal and altered fatty acid metabolism. Am J Kidney Dis 41:S4-S12, 2003 (suppl 4)

192. Bohmer T, Bergrem H, Eiklid K: Carnitine deficiency induced during intermittent haemodialysis for renal failure. Lancet 1:126-128, 1978

193. Golper TA, Goral S, Becker BN, Langman CB: L-Carnitine treatment of anemia. Am J Kidney Dis 41:S27-S34, 2003 (suppl 4)

194. Berns JS, Mosenkis A: Pharmacologic adjuvants to epoetin in the treatment of anemia in patients on hemodialysis. Hemodial Int 9:7-22, 2005

195. Levocarnitine for Use in the Treatment of Carnitine Deficiency in ESRD Patients (program memorandum). Baltimore, MD, Department of Health & Human Services (DHHS), Centers for Medicare & Medicaid Services (CMS), 2003

196. Caruso U, Leone L, Cravotto E, Nava D: Effects of L-carnitine on anemia in aged hemodialysis patients treated with recombinant human erythropoietin: A pilot study. Dial Transplant 27:498-506, 1998

197. Kletzmayr J, Sunder-Plassmann G, Horl WH: High dose intravenous iron: A note of caution. Nephrol Dial Transplant 17:962-965, 2002

198. Labonia WD: L-Carnitine effects on anemia in hemodialyzed patients treated with erythropoietin. Am J Kidney Dis 26:757-764, 1995

199. Semeniuk J, Shalansky KF, Taylor N, Jastrzebski J, Cameron EC: Evaluation of the effect of intravenous L-carnitine on quality of life in chronic hemodialysis patients. Clin Nephrol 54:470-477, 2000

200. Vaux EC, Taylor DJ, Altmann P, et al: Effects of carnitine supplementation on muscle metabolism by the use of magnetic resonance spectroscopy and near-infrared spectroscopy in end-stage renal disease. Nephron Clin Pract 97:c41-c48, 2004

200a. Steiber AL, Davis AT, Spry L, Strong J, Buss AL, Ratkiewicz MM, Weatherspoon LJ: Carnitine treatment improved quality-of-life measure in a sample of Midwestern hemodialysis patients. JPEN J Parenter Enteral Nutr 2006 Jan-Feb; 30(1):10-5.

201. Hurot JM, Cucherat M, Haugh M, Fouque D: Effects of L-carnitine supplementation in maintenance hemodialysis patients: A systematic review. J Am Soc Nephrol 13:708-714, 2002

202. Eknoyan G, Latos DL, Lindberg J: Practice recommendations for the use of L-carnitine in dialysis-related carnitine disorder. National Kidney Foundation Carnitine Consensus Conference. Am J Kidney Dis 41:868-876, 2003

203. National Kidney Foundation: K/DOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure. Am J Kidney Dis 35:S66-S70, 2000 (suppl 2)

204. Bridges KR, Hoffman KE: The effects of ascorbic acid on the intracellular metabolism of iron and ferritin. J Biol Chem 261:14273-14277, 1986

205. Lipschitz DA, Bothwell TH, Seftel HC, Wapnick AA, Charlton RW: The role of ascorbic acid in the metabolism of storage iron. Br J Haematol 20:155-163, 1971

206. Descombes E, Hanck AB, Fellay G: Water soluble vitamins in chronic hemodialysis patients and need for supplementation. Kidney Int 43:1319-1328, 1993

207. Sullivan JF, Eisenstein AB, Mottola OM, Mittal AK: The effect of dialysis on plasma and tissue levels of vitamin C. Trans Am Soc Artif Intern Organs 18:277-282, 1972

208. Costello JF, Sadovnic MJ, Cottington EM: Plasma oxalate levels rise in hemodialysis patients despite increased oxalate removal. J Am Soc Nephrol 1:1289-1298, 1991

209. Gastaldello K, Vereerstraeten A, Nzame-Nze T, Vanherweghem JL, Tielemans C: Resistance to erythropoietin in iron-overloaded haemodialysis patients can be overcome by ascorbic acid administration. Nephrol Dial Transplant 10:S44-S47, 1995 (suppl 6)

210. Lin CL, Hsu PY, Yang HY, Huang CC: Low dose intravenous ascorbic acid for erythropoietin-hyporesponsive anemia in diabetic hemodialysis patients with iron overload. Ren Fail 25:445-453, 2003

211. Sezer S, Ozdemir FN, Yakupoglu U, Arat Z, Turan M, Haberal M: Intravenous ascorbic acid administration for erythropoietin-hyporesponsive anemia in iron loaded hemodialysis patients. Artif Organs 26:366-370, 2002

212. Tarng DC, Huang TP: A parallel, comparative study of intravenous iron versus intravenous ascorbic acid for erythropoietin-hyporesponsive anaemia in haemodialysis patients with iron overload. Nephrol Dial Transplant 13:2867-2872, 1998

213. Tarng DC, Wei YH, Huang TP, Kuo BI, Yang WC: Intravenous ascorbic acid as an adjuvant therapy for recombinant erythropoietin in hemodialysis patients with hyperferritinemia. Kidney Int 55:2477-2486, 1999

214. Giancaspro V, Nuzziello M, Pallotta G, Sacchetti A, Petrarulo F: Intravenous ascorbic acid in hemodialysis patients with functional iron deficiency: A clinical trial. J Nephrol 13:444-449, 2000

215. Deira J, Diego J, Martinez R, et al: Comparative study of intravenous ascorbic acid versus low-dose desferroxamine in patients on hemodialysis with hyperferritinemia. J Nephrol 16:703-709, 2003

216. Mydlik M, Derzsiova K, Boldizsar J, Hribikova M, Petrovicova J: Oral use of iron with vitamin C in hemodialyzed patients. J Ren Nutr 13:47-51, 2003

217. Nguyen TV: Oral ascorbic acid as adjuvant to epoetin alfa in hemodialysis patients with hyperferritinemia. Am J Health Syst Pharm 61:2007-2008, 2004

218. Tovbin D, Markowitz A, Mostoslavsky M, Landver R: Effectiveness of erythropoiesis on supervised intradialytic oral iron and vitamin C therapy is correlated with Kt/V and patient weight. Clin Nephrol 53:276-282, 2000

219. Chan D, Irish A, Dogra G: Efficacy and safety of oral versus intravenous ascorbic acid for anaemia in haemodialysis patients. Nephrology (Carlton) 10:336-340, 2005

220. Balcke P, Schmidt P, Zazgornik J, Kopsa H, Haubenstock A: Ascorbic acid aggravates secondary hyperoxalemia in patients on chronic hemodialysis. Ann Intern Med 101:344-345, 1984

221. Pru C, Eaton J, Kjellstrand C: Vitamin C intoxication and hyperoxalemia in chronic hemodialysis patients. Nephron 39:112-116, 1985

222. Canavese C, Petrarulo M, Massarenti P, et al: Long-term, low-dose, intravenous vitamin C leads to plasma calcium oxalate supersaturation in hemodialysis patients. Am J Kidney Dis 45:540-549, 2005

223. Berger TM, Polidori MC, Dabbagh A, et al: Antioxidant activity of vitamin C in iron-overloaded human plasma. J Biol Chem 272:15656-15660, 1997

224. Chen WT, Lin YF, Yu FC, Kao WY, Huang WH, Yan HC: Effect of ascorbic acid administration in hemodialysis patients on in vitro oxidative stress parameters: Influence of serum ferritin levels. Am J Kidney Dis 42:158-166, 2003

225. Sirken G, Kung SC, Raja R: Decreased erythropoietin requirements in maintenance hemodialysis patients with statin therapy. ASAIO J 49:422-425, 2003

226. Cooper A, Mikhail A, Lethbridge MW, Kemeny DM, Macdougall IC: Pentoxifylline improves hemoglobin levels

in patients with erythropoietin-resistant anemia in renal failure. J Am Soc Nephrol 15:1877-1882, 2004

227. Weissgarten J, Modai D, Oz D, et al: Vitamin B(6) therapy does not improve hematocrit in hemodialysis patients supplemented with iron and erythropoietin. Nephron 87:328-332, 2001

228. Ayli D, Ayli M, Azak A, et al: The effect of high-flux hemodialysis on renal anemia. J Nephrol 17:701-706, 2004

229. Locatelli F, Andrulli S, Pecchini F, et al: Effect of high-flux dialysis on the anaemia of haemodialysis patients. Nephrol Dial Transplant 15:1399-1409, 2000

230. Opatrny K Jr, Reischig T, Vienken J, et al: Does treatment modality have an impact on anemia in patients with chronic renal failure? Effect of low- and high-flux biocompatible dialysis. Artif Organs 26:181-188, 2002

231. Richardson D, Lindley EJ, Bartlett C, Will EJ: A randomized, controlled study of the consequences of hemodialysis membrane composition on erythropoietic response. Am J Kidney Dis 42:551-560, 2003

232. Ifudu O, Feldman J, Friedman EA: The intensity of hemodialysis and the response to erythropoietin in patients with end-stage renal disease. N Engl J Med 334:420-425, 1996

233. Ifudu O, Uribarri J, Rajwani I, et al: Adequacy of dialysis and differences in hematocrit among dialysis facilities. Am J Kidney Dis 36:1166-1174, 2000

234. Madore F, Lowrie EG, Brugnara C, et al: Anemia in hemodialysis patients: Variables affecting this outcome predictor. J Am Soc Nephrol 8:1921-1929, 1997

235. Movilli E, Cancarini GC, Vizzardi V, et al: Epoetin requirement does not depend on dialysis dose when Kt/V $>$ 1.33 in patients on regular dialysis treatment with cellulosic membranes and adequate iron stores. J Nephrol 16:546-551, 2003

236. Movilli E, Cancarini GC, Zani R, Camerini C, Sandrini M, Maiorca R: Adequacy of dialysis reduces the doses of recombinant erythropoietin independently from the use of biocompatible membranes in haemodialysis patients. Nephrol Dial Transplant 16:111-114, 2001

237. Kobayashi S, Moriya H, Aso K, Ohtake T: Vitamin E-bonded hemodialyzer improves atherosclerosis associated with a rheological improvement of circulating red blood cells. Kidney Int 63:1881-1887, 2003

238. Miller ER III, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E: Meta-analysis: High-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med 142:37-46, 2005

239. Ward RA: Ultrapure dialysate. Semin Dial 17:489-497, 2004

240. Ward RA: Ultrapure dialysate: A desirable and achievable goal for routine hemodialysis. Semin Dial 13:378-380, 2000

241. Kleophas W, Haastert B, Backus G, Hilgers P, Westhoff A, van Endert G: Long-term experience with an ultrapure individual dialysis fluid with a batch type machine. Nephrol Dial Transplant 13:3118-3125, 1998

242. Hsu PY, Lin CL, Yu CC, et al: Ultrapure dialysate improves iron utilization and erythropoietin response in chronic hemodialysis patients—A prospective cross-over study. J Nephrol 17:693-700, 2004

243. Schiffl H, Lang SM, Bergner A: Ultrapure dialysate reduces dose of recombinant human erythropoietin. Nephron 83:278-279, 1999

244. Sitter T, Bergner A, Schiffl H: Dialysate related cytokine induction and response to recombinant human erythropoietin in haemodialysis patients. Nephrol Dial Transplant 15:1207-1211, 2000

245. Eiselt J, Racek J, Opatrny K Jr: The effect of hemodialysis and acetate-free biofiltration on anemia. Int J Artif Organs 23:173-180, 2000

246. Ward RA, Schmidt B, Hullin J, Hillebrand GF, Samtleben W: A comparison of on-line hemodiafiltration and high-flux hemodialysis: A prospective clinical study. J Am Soc Nephrol 11:2344-2350, 2000

247. Wizemann V, Lotz C, Techert F, Uthoff S: On-line haemodiafiltration versus low-flux haemodialysis. A prospective randomized study. Nephrol Dial Transplant 15:S43-S48, 2000 (suppl 1)

248. Maduell F, del Pozo C, Garcia H, et al: Change from conventional haemodiafiltration to on-line haemodiafiltration. Nephrol Dial Transplant 14:1202-1207, 1999

249. Lindsay RM: The London, Ontario, Daily/Nocturnal Hemodialysis Study. Semin Dial 17:85-91, 2004

250. Ting GO, Kjellstrand C, Freitas T, Carrie BJ, Zarghamee S: Long-term study of high-comorbidity ESRD patients converted from conventional to short daily hemodialysis. Am J Kidney Dis 42:1020-1035, 2003

251. Rao M, Muirhead N, Klarenbach S, Moist L, Lindsay RM: Management of anemia with quotidian hemodialysis. Am J Kidney Dis 42:18-23, 2003

252. Schwartz DI, Pierratos A, Richardson RM, Fenton SS, Chan CT: Impact of nocturnal home hemodialysis on anemia management in patients with end-stage renal disease. Clin Nephrol 63:202-208, 2005

253. Woods JD, Port FK, Orzol S, et al: Clinical and biochemical correlates of starting "daily" hemodialysis. Kidney Int 55:2467-2476, 1999

254. Yuen D, Richardson RM, Fenton SS, McGrath-Chong ME, Chan CT: Quotidian nocturnal hemodialysis improves cytokine profile and enhances erythropoietin responsiveness. ASAIO J 51:236-241, 2005

255. Coronel F, Herrero JA, Montenegro J, et al: Erythropoietin requirements: A comparative multicenter study between peritoneal dialysis and hemodialysis. J Nephrol 16:697-702, 2003

256. Snyder JJ, Foley RN, Gilbertson DT, Vonesh EF, Collins AJ: Hemoglobin levels and erythropoietin doses in hemodialysis and peritoneal dialysis patients in the United States. J Am Soc Nephrol 15:174-179, 2004

257. Taji Y, Morimoto T, Okada K, Fukuhara S, Fukui T, Kuwahara T: Effects of intravenous ascorbic acid on erythropoiesis and quality of life in unselected hemodialysis patients. J Nephrol 17:537-543, 2004

258. Keven K, Kutlay S, Nergizoglu G, Erturk S: Randomized, crossover study of the effect of vitamin C on EPO response in hemodialysis patients. Am J Kidney Dis 41:1233-1239, 2003

259. Sheashaa H, Abdel-Razek W, El-Husseini A, et al: Use of nandrolone decanoate as an adjuvant for erythropoietin dose reduction in treating anemia in patients on hemodialysis. Nephron Clin Pract 99:c102-c106, 2005

260. Gaughan WJ, Liss KA, Dunn SR, et al: A 6-month study of low-dose recombinant human erythropoietin alone and in combination with androgens for the treatment of anemia in chronic hemodialysis patients. Am J Kidney Dis 30:495-500, 1997

261. Berns JS, Rudnick MR, Cohen RM: A controlled trial of recombinant human erythropoietin and nandrolone decanoate in the treatment of anemia in patients on chronic hemodialysis. Clin Nephrol 37:264-267, 1992

262. McCullough PA, Lepor NE: The deadly triangle of anemia, renal insufficiency, and cardiovascular disease: implications for prognosis and treatment. Rev Cardiovasc Med 6:1-10, 2005

263. Linman JW: Physiologic and pathophysiologic effects of anemia. N Engl J Med 279:812-818, 1968

264. Rao SV, Jollis JG, Harrington RA, et al: Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. JAMA 292:1555-1562, 2004

265. House AA, Pham B, Page DE: Transfusion and recombinant human erythropoietin requirements differ between dialysis modalities. Nephrol Dial Transplant 13:1763-1769, 1998

266. Popovsky MA, Ransil BJ: Long-term impact of recombinant human erythropoietin on transfusion support in patients with chronic renal failure. Immunohematology 12:1-3, 1996

267. Eschbach JW: The anemia of chronic renal failure: Pathophysiology and the effects of recombinant erythropoietin. Kidney Int 35:134-148, 1989

268. European Best Practice Guidelines for Renal Transplantation (part 1). Nephrol Dial Transplant 15:S1-S85, 2000 (suppl 7)

269. Welch HG, Meehan KR, Goodnough LT: Prudent strategies for elective red blood cell transfusion. Ann Intern Med 116:393-402, 1992

270. American College of Physicians: Practice strategies for elective red blood cell transfusion. Ann Intern Med 116:403-406, 1992

271. Crosby E, Ferguson D, Hume HA, Kronick JB, Larke B, LeBlond P, et al: Guidelines for red blood cell and plasma transfusion for adults and children. CMAJ 156:S1-S24, 1997 (suppl 11)

272. Ifudu O, Macey LJ, Friedman EA: Resurgence of blood transfusion therapy in erythropoietin treated hemodialysis patients. ASAIO J 41:M426-M430, 1995

273. Casadevall N, Nataf J, Viron B, et al: Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. N Engl J Med 346:469-475, 2002

274. Rossert J, Casadevall N, Eckardt KU: Anti-erythropoietin antibodies and pure red cell aplasia. J Am Soc Nephrol 15:398-406, 2004

275. Boven K, Stryker S, Knight J, et al: The increased incidence of pure red cell aplasia with an Eprex formulation in uncoated rubber stopper syringes. Kidney Int 67:2346-2353, 2005

276. Eckardt KU, Casadevall N: Pure red-cell aplasia due to anti-erythropoietin antibodies. Nephrol Dial Transplant 18:865-869, 2003

277. Casadevall N, Cournoyer D, Marsh J, et al: Recommendations on haematological criteria for the diagnosis of epoetin-induced pure red cell aplasia. Eur J Haematol 73:389-396, 2004

278. Bennett CL, Luminari S, Nissenson AR, et al: Pure red-cell aplasia and epoetin therapy. N Engl J Med 351:1403-1408, 2004

279. Cournoyer D, Toffelmire EB, Wells GA, et al: Anti-erythropoietin antibody-mediated pure red cell aplasia after treatment with recombinant erythropoietin products: Recommendations for minimization of risk. J Am Soc Nephrol 15:2728-2734, 2004

280. Kausz AT, Solid C, Pereira BJ, Collins AJ, St Peter W: Intractable anemia among hemodialysis patients: A sign of suboptimal management or a marker of disease? Am J Kidney Dis 45:136-147, 2005

281. Cheng IK, Lu HB, Wei DC, Cheng SW, Chan CY, Lee FC: Influence of thalassemia on the response to recombinant human erythropoietin in dialysis patients. Am J Nephrol 13:142-148, 1993

282. Di Iorio B, Guastaferro P, Bellizzi V: Relationship between resistance to erythropoietin and high anomalous hemoglobin levels in hemodialysis patients with beta-thalassemia minor. Blood Purif 21:376-380, 2003

283. Lai KN, Wong KC, Li PK, Lui SF: Use of recombinant erythropoietin in thalassemic patients on dialysis. Am J Kidney Dis 19:239-245, 1992

284. Di Iorio B, De Nicola L, Bellizzi V, et al: Efficacy of erythropoietin on dialysis in patients with beta thalassemia minor. Blood Purif 22:453-460, 2004

285. Paritpokee N, Wiwanitkit V, Bhokaisawan N, Boonchalermvichian C, Preechakas P: Serum erythropoietin levels in pediatric patients with beta-thalassemia/hemoglobin E. Clin Lab 48:631-634, 2002

286. Katopodis KP, Elisaf MS, Pappas HA, et al: Renal abnormalities in patients with sickle cell-beta thalassemia. J Nephrol 10:163-167, 1997

287. Papassotiriou I, Traeger-Synodinos J, Kanavakis E, Karagiorga M, Stamoulakatou A, Kattamis C: Erythroid marrow activity and hemoglobin H levels in hemoglobin H disease. J Pediatr Hematol Oncol 20:539-544, 1998

288. Powe NR, Griffiths RI, Greer JW, et al: Early dosing practices and effectiveness of recombinant human erythropoietin. Kidney Int 43:1125-1133, 1993

289. Tomson CR, Edmunds ME, Chambers K, Bricknell S, Feehally J, Walls J: Effect of recombinant human erythropoietin on erythropoiesis in homozygous sickle-cell anaemia and renal failure. Nephrol Dial Transplant 7:817-821, 1992

290. Papassotiriou I, Voskaridou E, Stamoulakatou A, Loukopoulos D: Increased erythropoietin level induced by hydroxyurea treatment of sickle cell patients. Hematol J 1:295-300, 2000

291. Dammacco F, Luccarelli G, Prete M, Silvestris F: The role of recombinant human erythropoietin alpha in the treatment of chronic anemia in multiple myeloma. Rev Clin Exp Hematol Suppl 1:S32-S38, 2002

292. Weber G, Gross J, Kromminga A, Loew HH, Eckardt KU: Allergic skin and systemic reactions in a patient with pure red cell aplasia and anti-erythropoietin antibodies challenged with different epoetins. J Am Soc Nephrol 13:2381-2383, 2002

293. Verhelst D, Rossert J, Casadevall N, Kruger A, Eckardt KU, Macdougall IC: Treatment of erythropoietin-

induced pure red cell aplasia: A retrospective study. Lancet 363:1768-1771, 2004

294. Rossert J, Macdougall I, Casadevall N: Antibody-mediated pure red cell aplasia (PRCA) treatment and re-treatment: Multiple options. Nephrol Dial Transplant 20:Siv23-Siv26, 2005 (suppl 4)

295. Asari A, Gokal R: Pure red cell aplasia secondary to epoetin alpha responding to darbepoetin alpha in a patient on peritoneal dialysis. J Am Soc Nephrol 15:2204-2207, 2004

296. Tarng DC, Chang JG, Huang TP: Resistance to recombinant erythropoietin in a hemodialysis patient with heterozygous hemoglobinopathy J-Meinung. Am J Kidney Dis 29:769-772, 1997

297. Drueke TB: Resistance to recombinant human erythropoietin in hemodialysis patients. Am J Nephrol 10:S34-S39, 1990 (suppl 2)

298. Ataga KI, Orringer EP: Renal abnormalities in sickle cell disease. Am J Hematol 63:205-211, 2000

299. Drueke TB: Modulating factors in the hematopoietic response to erythropoietin. Am J Kidney Dis 18:87-92, 1991

300. Yorgin PD, Belson A, Al-Uzri AY, Alexander SR: The clinical efficacy of higher hematocrit levels in children with chronic renal insufficiency and those undergoing dialysis. Semin Nephrol 21:451-462, 2001

301. Greenbaum LA: Anemia management in children, in Nissenson AR, Fine RN (eds): Clinical Dialysis. New York, NY, McGraw Hill, 2005, pp 1111-1134

302. McGonigle RJ, Boineau FG, Beckman B, et al: Erythropoietin and inhibitors of in vitro erythropoiesis in the development of anemia in children with renal disease. J Lab Clin Med 105:449-458, 1985

303. Nathan DG, Orkin SH: Appendix 11. Normal hematologic values in children, in Nathan DG, Orkin SH, Ginsburg D, Look AT, Oski FA (eds): Nathan and Oski's Hematology of Infancy and Childhood (ed 6). Philadelphia, PA, Saunders, 2003, p 1841

304. Warady BA, Kausz A, Lerner G, et al: Iron therapy in the pediatric hemodialysis population. Pediatr Nephrol 19: 655-661, 2004

305. Warady BA, Zobrist RH, Wu J, Finan E: Sodium ferric gluconate complex therapy in anemic children on hemodialysis. Pediatr Nephrol 20:1320-1327, 2005

306. Warady BA, Ho M: Morbidity and mortality in children with anemia at initiation of dialysis. Pediatr Nephrol 18:1055-1062, 2003

307. Mitsnefes MM, Daniels SR, Schwartz SM, Meyer RA, Khoury P, Strife CF: Severe left ventricular hypertrophy in pediatric dialysis: Prevalence and predictors. Pediatr Nephrol 14:898-902, 2000

308. Mitsnefes MM, Kimball TR, Border WL, et al: Impaired left ventricular diastolic function in children with chronic renal failure. Kidney Int 65:1461-1466, 2004

309. Martin GR, Ongkingo JR, Turner ME, Skurow ES, Ruley EJ: Recombinant erythropoietin (Epogen) improves cardiac exercise performance in children with end-stage renal disease. Pediatr Nephrol 7:276-280, 1993

310. Baraldi E, Montini G, Zanconato S, Zacchello G, Zacchello F: Exercise tolerance after anaemia correction with recombinant human erythropoietin in end-stage renal disease. Pediatr Nephrol 4:623-626, 1990

311. Bassi S, Montini G, Edefonti A, et al: Cardiovascular function in a chronic peritoneal dialysis pediatric population on recombinant human erythropoietin treatment. Perit Dial Int 13:S267-S269, 1993 (suppl 2)

312. Gerson A, Hwang W, Fiorenza J, et al: Anemia and health-related quality of life in adolescents with chronic kidney disease. Am J Kidney Dis 44:1017-1023, 2004

313. Van Damme-Lombaerts R, Broyer M, Businger J, Baldauf C, Stocker H: A study of recombinant human erythropoietin in the treatment of anaemia of chronic renal failure in children on haemodialysis. Pediatr Nephrol 8:338-342, 1994

314. Kurtin PS, Landgraf JM, Abetz L: Patient-based health status measurements in pediatric dialysis: Expanding the assessment of outcome. Am J Kidney Dis 24:376-382, 1994

315. Halterman JS, Kaczorowski JM, Aligne CA, Auinger P, Szilagyi PG: Iron deficiency and cognitive achievement among school-aged children and adolescents in the United States. Pediatrics 107:1381-1386, 2001

316. Burke JR: Low-dose subcutaneous recombinant erythropoietin in children with chronic renal failure. Australian and New Zealand Paediatric Nephrology Association. Pediatr Nephrol 9:558-561, 1995

317. Jabs K: The effects of recombinant human erythropoietin on growth and nutritional status. Pediatr Nephrol 10:324-327, 1996

318. Scigalla P, Bonzel KE, Bulla M, et al: Therapy of renal anemia with recombinant human erythropoietin in children with end-stage renal disease. Contrib Nephrol 76:227-240; discussion 240-221, 1989

319. Brandt JR, Avner ED, Hickman RO, Watkins SL: Safety and efficacy of erythropoietin in children with chronic renal failure. Pediatr Nephrol 13:143-147, 1999

320. Burghard R, Gordjani N, Leititis JU: [Treatment of renal anemia with recombinant human erythropoietin]. Monatsschr Kinderheilkd 137:174-177, 1989

321. Campos A, Garin EH: Therapy of renal anemia in children and adolescents with recombinant human erythropoietin (rHuEPO). Clin Pediatr (Phila) 31:94-99, 1992

322. Offner G, Hoyer PF, Latta K, Winkler L, Brodehl J, Scigalla P: One year's experience with recombinant erythropoietin in children undergoing continuous ambulatory or cycling peritoneal dialysis. Pediatr Nephrol 4:498-500, 1990

323. Sinai-Trieman L, Salusky IB, Fine RN: Use of subcutaneous recombinant human erythropoietin in children undergoing continuous cycling peritoneal dialysis. J Pediatr 114:550-554, 1989

324. Eschbach JW, Adamson JW: Guidelines for recombinant human erythropoietin therapy. Am J Kidney Dis 14:2-8, 1989

325. North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) 2004 Annual Report. Boston, MA, NAPRTCS Administrative Office, 2004

326. Sieniawska M, Roszkowska-Blaim M: Recombinant human erythropoietin dosage in children undergoing hemodialysis and continuous ambulatory peritoneal dialysis. Pediatr Nephrol 11:628-630, 1997

327. Port RE, Kiepe D, Van Guilder M, Jelliffe RW, Mehls O: Recombinant human erythropoietin for the treatment of renal anaemia in children: no justification for

bodyweight-adjusted dosage. Clin Pharmacokinet 43:57-70, 2004

328. Juul SE: Nonerythropoietic roles of erythropoietin in the fetus and neonate. Clin Perinatol 27:527-541, 2000

329. De Palo T, Giordano M, Palumbo F, et al: Clinical experience with darbepoietin alfa (NESP) in children undergoing hemodialysis. Pediatr Nephrol 19:337-340, 2004

330. Lerner G, Kale AS, Warady BA, et al: Pharmacokinetics of darbepoetin alfa in pediatric patients with chronic kidney disease. Pediatr Nephrol 17:933-937, 2002

331. Geary DF, Keating LE, Vigneux A, Stephens D, Hebert D, Harvey EA: Darbepoetin alfa (Aranesp) in children with chronic renal failure. Kidney Int 68:1759-1765, 2005

332. Bald M, Holder M, Leichter HE: Improved therapy of renal anemia after switching to darbepoietin (NESP) in peritoneal dialysis patients. Pediatr Nephrol 9:249A, 2002 (abstr)

333. Scharer K, Klare B, Braun A, Dressel P, Gretz N: Treatment of renal anemia by subcutaneous erythropoietin in children with preterminal chronic renal failure. Acta Paediatr 82:953-958, 1993

334. Yalcinkaya F, Tumer N, Cakar N, Ozkaya N: Low-dose erythropoietin is effective and safe in children on continuous ambulatory peritoneal dialysis. Pediatr Nephrol 11:350-352, 1997

335. Schroder CH: The management of anemia in pediatric peritoneal dialysis patients. Guidelines by an ad hoc European committee. Pediatr Nephrol 18:805-809, 2003

336. Van Damme-Lombaerts R, Herman J: Erythropoietin treatment in children with renal failure. Pediatr Nephrol 13:148-152, 1999

337. Gershanik J, Boecler B, Ensley H, McCloskey S, George W: The gasping syndrome and benzyl alcohol poisoning. N Engl J Med 307:1384-1388, 1982

338. Hiller JL, Benda GI, Rahatzad M, et al: Benzyl alcohol toxicity: impact on mortality and intraventricular hemorrhage among very low birth weight infants. Pediatrics 77:500-506, 1986

339. Evans JH, Brocklebank JT, Bowmer CJ, Ng PC: Pharmacokinetics of recombinant human erythropoietin in children with renal failure. Nephrol Dial Transplant 6:709-714, 1991

340. Reddingius RE, Schroder CH, Koster AM, Monnens LA: Pharmacokinetics of recombinant human erythropoietin in children treated with continuous ambulatory peritoneal dialysis. Eur J Pediatr 153:850-854, 1994

341. Seeherunvong W, Rubio L, Abitbol CL, et al: Identification of poor responders to erythropoietin among children undergoing hemodialysis. J Pediatr 138:710-714, 2001

342. Muller-Wiefel DE, Sinn H, Gilli G, Scharer K: Hemolysis and blood loss in children with chronic renal failure. Clin Nephrol 8:481-486, 1977

343. Gillespie RS, Wolf FM: Intravenous iron therapy in pediatric hemodialysis patients: A meta-analysis. Pediatr Nephrol 19:662-666, 2004

344. Morgan HE, Gautam M, Geary DF: Maintenance intravenous iron therapy in pediatric hemodialysis patients. Pediatr Nephrol 16:779-783, 2001

345. Cook JD, Carriaga M, Kahn SG, Schalch W, Skikne BS: Gastric delivery system for iron supplementation. Lancet 335:1136-1139, 1990

346. Goch J, Birgegard G, Danielson BG, Wikstrom B: Iron absorption in patients with chronic uremia on maintenance hemodialysis and in healthy volunteers measured with a simple oral iron load test. Nephron 73:403-406, 1996

347. Ruiz-Jaramillo Mde L, Guizar-Mendoza JM, Gutierrez-Navarro Mde J, Dubey-Ortega LA, Amador-Licona N: Intermittent versus maintenance iron therapy in children on hemodialysis: A randomized study. Pediatr Nephrol 19:77-81, 2004

348. Greenbaum LA, Pan CG, Caley C, Nelson T, Sheth KJ: Intravenous iron dextran and erythropoietin use in pediatric hemodialysis patients. Pediatr Nephrol 14:908-911, 2000

349. Frankenfield DL, Neu AM, Warady BA, Fivush BA, Johnson CA, Brem AS: Anemia in pediatric hemodialysis patients: Results from the 2001 ESRD Clinical Performance Measures Project. Kidney Int 64:1120-1124, 2003

350. Tenbrock K, Muller-Berghaus J, Michalk D, Querfeld U: Intravenous iron treatment of renal anemia in children on hemodialysis. Pediatr Nephrol 13:580-582, 1999

351. Morris KP, Watson S, Reid MM, Hamilton PJ, Coulthard MG: Assessing iron status in children with chronic renal failure on erythropoietin: Which measurements should we use? Pediatr Nephrol 8:51-56, 1994

352. Brugnara C, Zurakowski D, DiCanzio J, Boyd T, Platt O: Reticulocyte hemoglobin content to diagnose iron deficiency in children. JAMA 281:2225-2230, 1999

353. Bothwell TH, Pirzio-Biroli G, Finch CA: Iron absorption. I. Factors influencing absorption. J Lab Clin Med 51:24-36, 1958

354. Yorgin PD, Belson A, Sarwal M, Alexander SR: Sodium ferric gluconate therapy in renal transplant and renal failure patients. Pediatr Nephrol 15:171-175, 2000

355. Danielson BG: Structure, chemistry, and pharmacokinetics of intravenous iron agents. J Am Soc Nephrol 15:S93-S98, 2004 (suppl 2)

356. Ahsan N: Intravenous infusion of total dose iron is superior to oral iron in treatment of anemia in peritoneal dialysis patients: A single center comparative study. J Am Soc Nephrol 9:664-668, 1998

357. Anuradha S, Singh NP, Agarwal SK: Total dose infusion iron dextran therapy in predialysis chronic renal failure patients. Ren Fail 24:307-313, 2002

358. Dahdah K, Patrie JT, Bolton WK: Intravenous iron dextran treatment in predialysis patients with chronic renal failure. Am J Kidney Dis 36:775-782, 2000

359. Domrongkitchaiporn S, Jirakranont B, Atamasrikul K, Ungkanont A, Bunyaratvej A: Indices of iron status in continuous ambulatory peritoneal dialysis patients. Am J Kidney Dis 34:29-35, 1999

360. Prakash S, Walele A, Dimkovic N, Bargman J, Vas S, Oreopoulos D: Experience with a large dose (500 mg) of intravenous iron dextran and iron saccharate in peritoneal dialysis patients. Perit Dial Int 21:290-295, 2001

361. Folkert VW, Michael B, Agarwal R, et al: Chronic use of sodium ferric gluconate complex in hemodialysis patients: safety of higher-dose ($>$ or $=$250 mg) administration. Am J Kidney Dis 41:651-657, 2003

362. Leijn E, Monnens LA, Cornelissen EA: Intravenous iron supplementation in children on hemodialysis. J Nephrol 17:423-426, 2004

363. Puntarulo S: Iron, oxidative stress and human health. Mol Aspects Med 26:299-312, 2005

364. Erdemoglu AK, Ozbakir S: Serum ferritin levels and early prognosis of stroke. Eur J Neurol 9:633-637, 2002

365. Gulcelik NE, Kayatas M: Importance of serum ferritin levels in patients with renal failure. Nephron 92:230-231, 2002

366. Gloggler A, Bulla M, Furst P: Effect of low dose supplementation of L-carnitine on lipid metabolism in hemodialyzed children. Kidney Int Suppl 27:S256-S258, 1989

367. Gloggler A, Bulla M, Puchstein C, Gulotta F, Furst P: Plasma and muscle carnitine in healthy and hemodialyzed children. Child Nephrol Urol 9:277-282, 1988

368. Zachwieja J, Duran M, Joles JA, et al: Amino acid and carnitine supplementation in haemodialysed children. Pediatr Nephrol 8:739-743, 1994

369. Murakami R, Momota T, Yoshiya K, et al: Serum carnitine and nutritional status in children treated with continuous ambulatory peritoneal dialysis. J Pediatr Gastroenterol Nutr 11:371-374, 1990

370. Warady BA, Borum P, Stall C, Millspaugh J, Taggart E, Lum G: Carnitine status of pediatric patients on continuous ambulatory peritoneal dialysis. Am J Nephrol 10:109-114, 1990

371. Berard E, Iordache A: Effect of low doses of L-carnitine on the response to recombinant human erythropoietin in hemodialyzed children: About two cases. Nephron 62:368-369, 1992

372. Lilien MR, Duran M, Quak JM, Frankhuisen JJ, Schroder CH: Oral L-carnitine does not decrease erythropoietin requirement in pediatric dialysis. Pediatr Nephrol 15:17-20, 2000

373. Goodman AM, Pollack MM, Patel KM, Luban NL: Pediatric red blood cell transfusions increase resource use. J Pediatr 142:123-127, 2003

374. Hume HA, Limoges P: Perioperative blood transfusion therapy in pediatric patients. Am J Ther 9:396-405, 2002

375. Niaudet P, Dudley J, Charbit M, Gagnadoux MF, Macleay K, Broyer M: Pretransplant blood transfusions with cyclosporine in pediatric renal transplantation. Pediatr Nephrol 14:451-456, 2000

376. Gill JS, Tonelli M, Mix CH, Pereira BJ: The change in allograft function among long-term kidney transplant recipients. J Am Soc Nephrol 14:1636-1642, 2003

377. Gill JS, Mix CH, Pereira BJ: Glomerular filtration rate and the prevalence of chronic kidney disease among transplant recipients in the United States. Am J Transplant 2:358A, 2002 (abstr)

377A. Levey AS, Eckardt KU, Tsukamoto Y, et al: Definition and classification of chronic kidney disease: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 67:2089-2100, 2005

378. Besarab A, Caro J, Jarrell BE, Francos G, Erslev AJ: Dynamics of erythropoiesis following renal transplantation. Kidney Int 32:526-536, 1987

379. Beshara S, Birgegard G, Goch J, Wahlberg J, Wikstrom B, Danielson BG: Assessment of erythropoiesis following renal transplantation. Eur J Haematol 58:167-173, 1997

380. Brown JH, Lappin TR, Elder GE, Taylor TN, Bridges JM, McGeown MG: The initiation of erythropoiesis following renal transplantation. Nephrol Dial Transplant 4:1076-1079, 1989

381. Moore LW, Smith SO, Winsett RP, Acchiardo SR, Gaber AO: Factors affecting erythropoietin production and correction of anemia in kidney transplant recipients. Clin Transplant 8:358-364, 1994

382. Sun CH, Ward HJ, Paul WL, Koyle MA, Yanagawa N, Lee DB: Serum erythropoietin levels after renal transplantation. N Engl J Med 321:151-157, 1989

383. Tornero F, Prats D, Alvarez-Sala JL, Coronel F, Sanchez A, Barrientos A: Iron deficiency anemia after successful renal transplantation. J Urol 149:1398-1400, 1993

384. Goch J, Birgegard G, Wikstrom B, Tufveson G, Danielson BG: Serum erythropoietin levels in the immediate kidney-posttransplant period. Nephron 60:30-34, 1992

385. Wolff M, Jelkmann W: Erythropoiesis and erythropoietin levels in renal transplant recipients. Klin Wochenschr 69:53-58, 1991

386. Nampoory MR, Johny KV, al-Hilali N, Seshadri MS, Kanagasabhapathy AS: Erythropoietin deficiency and relative resistance cause anaemia in post-renal transplant recipients with normal renal function. Nephrol Dial Transplant 11:177-181, 1996

387. Van Loo A, Vanholder R, Bernaert P, De Roose J, Lameire N: Recombinant human erythropoietin corrects anaemia during the first weeks after renal transplantation: A randomized prospective study. Nephrol Dial Transplant 11:1815-1821, 1996

388. Arbeiter K, Greenbaum L, Balzar E, et al: Reproducible erythroid aplasia caused by mycophenolate mofetil. Pediatr Nephrol 14:195-197, 2000

389. Kessler M: Erythropoietin and erythropoiesis in renal transplantation. Nephrol Dial Transplant 10:S114-S116, 1995 (suppl 6)

390. Eckardt KU, Frei U, Kliem V, Bauer C, Koch KM, Kurtz A: Role of excretory graft function for erythropoietin formation after renal transplantation. Eur J Clin Invest 20:563-572, 1990

391. Lee DB: Interrelationship between erythropoietin and erythropoiesis: Insights from renal transplantation. Am J Kidney Dis 18:54-56, 1991

392. Muirhead N: Erythropoietin and renal transplantation. Kidney Int Suppl 69:S86-S92, 1999

393. Yorgin PD, Scandling JD, Belson A, Sanchez J, Alexander SR, Andreoni KA: Late post-transplant anemia in adult renal transplant recipients. An under-recognized problem? Am J Transplant 2:429-435, 2002

394. Yorgin PD, Belson A, Sanchez J, et al: Unexpectedly high prevalence of posttransplant anemia in pediatric and young adult renal transplant recipients. Am J Kidney Dis 40:1306-1318, 2002

395. Vanrenterghem Y, Ponticelli C, Morales JM, et al: Prevalence and management of anemia in renal transplant recipients: A European survey. Am J Transplant 3:835-845, 2003

395A. Gill JS, Solid C, Pereira BJG, Collins AJ: Anemia management prior to kidney transplantation and the risk of post-transplant blood transfusion. Am J Transplant 4:S484, 2004 (suppl 8) (abstr 1191)

396. Saito S, Fujiwara T, Sakagami K, Matsuno T, Tanaka N: Anemia following renal transplantation. Transplant Proc 30:3025-3026, 1998

397. Saito S, Fujiwara T, Sakagami K, Matsuno T, Tanaka N: Anemia following renal transplantation. Transplant Proc 30:3025-3026., 1998

398. Mix TC, Kazmi W, Khan S, et al: Anemia: A continuing problem following kidney transplantation. Am J Transplant 3:1426-1433, 2003

399. Lorenz M, Kletzmayr J, Perschl A, Furrer A, Horl WH, Sunder-Plassmann G: Anemia and iron deficiencies among long-term renal transplant recipients. J Am Soc Nephrol 13:794-797, 2002

400. Winkelmayer WC, Kewalramani R, Rutstein M, Gabardi S, Vonvisger T, Chandraker A: Pharmacoepidemiology of anemia in kidney transplant recipients. J Am Soc Nephrol 15:1347-1352, 2004

401. Shibagaki Y, Shetty A: Anaemia is common after kidney transplantation, especially among African Americans. Nephrol Dial Transplant 19:2368-2373, 2004

402. Kausman JY, Powell HR, Jones CL: Anemia in pediatric renal transplant recipients. Pediatr Nephrol 19:526-530, 2004

403. Karthikeyan V, Karpinski J, Nair RC, Knoll G: The burden of chronic kidney disease in renal transplant recipients. Am J Transplant 4:262-269, 2004

404. Miles AM, Markell MS, Daskalakis P, et al: Anemia following renal transplantation: Erythropoietin response and iron deficiency. Clin Transplant 11:313-315, 1997

405. Teruel JL, Lamas S, Vila T, et al: Serum ferritin levels after renal transplantation: A prospective study. Nephron 51: 462-465, 1989

406. Moulin B, Ollier J, George F, et al: Serum erythropoietin and reticulocyte maturity index after renal transplantation: A prospective longitudinal study. Nephron 69:259-266, 1995

407. Chua MS, Barry C, Chen X, Salvatierra O, Sarwal MM: Molecular profiling of anemia in acute renal allograft rejection using DNA microarrays. Am J Transplant 3:17-22, 2003

408. Creemers GJ, van Boven WP, Lowenberg B, van der Heul C: Azathioprine-associated pure red cell aplasia. J Intern Med 233:85-87, 1993

409. Pruijt JF, Haanen JB, Hollander AA, den Ottolander GJ: Azathioprine-induced pure red-cell aplasia. Nephrol Dial Transplant 11:1371-1373, 1996

410. Abraham KA, Little MA, Dorman AM, Walshe JJ: Hemolytic-uremic syndrome in association with both cyclosporine and tacrolimus. Transpl Int 13:443-447, 2000

411. Epstein M, Landsberg D: Cyclosporine-induced thrombotic microangiopathy resulting in renal allograft loss and its successful reuse: A report of two cases. Am J Kidney Dis 17:346-348, 1991

412. Pham PT, Peng A, Wilkinson AH, et al: Cyclosporine and tacrolimus-associated thrombotic microangiopathy. Am J Kidney Dis 36:844-850, 2000

413. Trimarchi HM, Truong LD, Brennan S, Gonzalez JM, Suki WN: FK506-associated thrombotic microangiopathy: Report of two cases and review of the literature. Transplantation 67:539-544, 1999

414. Zarifian A, Meleg-Smith S, O'Donovan R, Tesi RJ, Batuman V: Cyclosporine-associated thrombotic microangiopathy in renal allografts. Kidney Int 55:2457-2466, 1999

415. Dussol B, Brunet P, Vacher-Coponat H, Saingra Y, Casanova P, Berland Y: Haemolytic uraemic syndrome in a renal transplant recipient during OKT3 therapy. Nephrol Dial Transplant 9:1191-1193, 1994

416. Morris-Stiff G, Evans M, Baboolal K, et al: Haemolytic uraemic syndrome associated with OKT3. Transpl Int 9:522-523, 1996

417. MacDonald AS: A worldwide, phase III, randomized, controlled, safety and efficacy study of a sirolimus/cyclosporine regimen for prevention of acute rejection in recipients of primary mismatched renal allografts. Transplantation 71:271-280, 2001

418. Kahan BD, Knight R, Schoenberg L, et al: Ten years of sirolimus therapy for human renal transplantation: The University of Texas at Houston experience. Transplant Proc 35:S25-S34, 2003 (suppl 3)

419. Augustine JJ, Knauss TC, Schulak JA, Bodziak KA, Siegel C, Hricik DE: Comparative effects of sirolimus and mycophenolate mofetil on erythropoiesis in kidney transplant patients. Am J Transplant 4:2001-2006, 2004

420. Crew RJ, Radhakrishnan J, Cohen DJ, et al: De novo thrombotic microangiopathy following treatment with sirolimus: Report of two cases. Nephrol Dial Transplant 20:203-209, 2005

421. Naito M, Kawashima A, Akiba T, Takanashi M, Nihei H: Effects of an angiotensin II receptor antagonist and angiotensin-converting enzyme inhibitors on burst forming units-erythroid in chronic hemodialysis patients. Am J Nephrol 23:287-293, 2003

422. Le Meur Y, Lorgeot V, Comte L, et al: Plasma levels and metabolism of AcSDKP in patients with chronic renal failure: Relationship with erythropoietin requirements. Am J Kidney Dis 38:510-517, 2001

423. So BJ, Chae KM, Lee KK, Lee YJ, Jeong BH: Pure red cell aplasia due to parvovirus B19 infection in a renal transplant patient: A case report. Transplant Proc 32:1954-1956, 2000

424. Vales-Albertos LJ, Garcia-Cardenas M, Chavez-Becerra S, Gomez-Navarro B, Monteon-Ramos F, Cueto-Manzano AM: Pure red cell aplasia associated with parvovirus B19 infection in renal transplantation: The first case report in Mexico. Transplantation 79:739, 2005 (abstr)

425. Karras A, Thervet E, Legendre C: Hemophagocytic syndrome in renal transplant recipients: Report of 17 cases and review of literature. Transplantation 77:238-243, 2004

426. Artz MA, Steenbergen EJ, Hoitsma AJ, Monnens LA, Wetzels JF: Renal transplantation in patients with hemolytic uremic syndrome: High rate of recurrence and increased incidence of acute rejections. Transplantation 76:821-826, 2003

427. Asaka M, Ishikawa I, Nakazawa T, Tomosugi N, Yuri T, Suzuki K: Hemolytic uremic syndrome associated with influenza A virus infection in an adult renal allograft recipient: Case report and review of the literature. Nephron 84:258-266, 2000

428. Waiser J, Budde K, Rudolph B, Ortner MA, Neumayer HH: De novo hemolytic uremic syndrome postrenal transplant after cytomegalovirus infection. Am J Kidney Dis 34:556-559, 1999

429. Laurence J, Mitra D, Steiner M, Staiano-Coico L, Jaffe E: Plasma from patients with idiopathic and human immunodeficiency virus-associated thrombotic thrombocytopenic purpura induces apoptosis in microvascular endothelial cells. Blood 87:3245-3254, 1996

430. Anagnostou A, Lee ES, Kessimian N, Levinson R, Steiner M: Erythropoietin has a mitogenic and positive chemotactic effect on endothelial cells. Proc Natl Acad Sci USA 87:5978-5982, 1990

431. Anagnostou A, Liu Z, Steiner M, et al: Erythropoietin receptor mRNA expression in human endothelial cells. Proc Natl Acad Sci U S A 91:3974-3978, 1994

432. Carlini RG, Alonzo EJ, Dominguez J, et al: Effect of recombinant human erythropoietin on endothelial cell apoptosis. Kidney Int 55:546-553, 1999

433. Debska-Slizien A, Chamienia A, Krol E, et al: Hemolytic anemia after renal transplantation: Analysis of case reports. Transplant Proc 35:2233-2237, 2003

434. Li FK, Chan TM, Lai KN: Alloimmune hemolysis after renal transplantation. Am J Nephrol 20:473-475, 2000

435. Peces R, Diaz Corte C, Navascues RA: [Hemolytic anemia caused by graft-versus-host reaction in ABO-nonidentical renal transplants from blood group O donors]. Nefrologia 21:395-401, 2001

436. Djamali A, Becker YT, Simmons WD, Johnson CA, Premasathian N, Becker BN: Increasing hematocrit reduces early posttransplant cardiovascular risk in diabetic transplant recipients. Transplantation 76:816-820, 2003

437. Rigatto C, Parfrey P, Foley R, Negrijn C, Tribula C, Jeffery J: Congestive heart failure in renal transplant recipients: Risk factors, outcomes, and relationship with ischemic heart disease. J Am Soc Nephrol 13:1084-1090, 2002

438. Rigatto C, Foley R, Jeffery J, Negrijn C, Tribula C, Parfrey P: Electrocardiographic left ventricular hypertrophy in renal transplant recipients: Prognostic value and impact of blood pressure and anemia. J Am Soc Nephrol 14:462-468, 2003

439. Winkelmayer WC, Lorenz M, Kramar R, Horl WH, Sunder-Plassmann G: Percentage of hypochromic red blood cells is an independent risk factor for mortality in kidney transplant recipients. Am J Transplant 4:2075-2081, 2004

440. Khan S, Tighiouart H, Kalra A, Raman G, Rohrer RJ, Pereira BJ: Resource utilization among kidney transplant recipients. Kidney Int 64:657-664, 2003

441. Schmidt R, Kupin W, Dumler F, Venkat KK, Mozes M: Influence of the pretransplant hematocrit level on early graft function in primary cadaveric renal transplantation. Transplantation 55:1034-1040, 1993

442. Vasquez EM, Pollak R: Effect of pretransplant erythropoietin therapy on renal allograft outcome. Transplantation 62:1026-1028, 1996

443. Paganini EP, Braun WE, Latham D, Abdulhadi MH: Renal transplantation: results in hemodialysis patients previously treated with recombinant human erythropoietin. ASAIO Trans 35:535-538, 1989

444. Van Biesen W, Vanholder R, Veys N, Verbeke F, Lameire N: Efficacy of erythropoietin administration in the treatment of anemia immediately after renal transplantation. Transplantation 79:367-368, 2005

444A. Nagarajan S, Vidhun J, Mansfield E, et al: Molecular mechanisms of transplant renal artery stenosis from early use of erythropoietin. Am J Transplant 4:S568-S569, 2004 (suppl 8)

445. Bagnis C, Beaufils H, Jacquiaud C, et al: Erythropoietin enhances recovery after cisplatin-induced acute renal failure in the rat. Nephrol Dial Transplant 16:932-938, 2001

446. Cerami A, Brines M, Ghezzi P, Cerami C, Itri LM: Neuroprotective properties of epoetin alfa. Nephrol Dial Transplant 17:S8-S12, 2002 (suppl 1)

447. Fishbane S, Ragolia L, Palaia T, Johnson B, Elzein H, Maesaka JK: Cytoprotection by darbepoetin/epoetin alfa in pig tubular and mouse mesangial cells. Kidney Int 65:452-458, 2004

448. Grimm C, Wenzel A, Groszer M, et al: HIF-1-induced erythropoietin in the hypoxic retina protects against light-induced retinal degeneration. Nat Med 8:718-724, 2002

449. Parsa CJ, Matsumoto A, Kim J, et al: A novel protective effect of erythropoietin in the infarcted heart. J Clin Invest 112:999-1007, 2003

450. Westenfelder C: Unexpected renal actions of erythropoietin. Exp Nephrol 10:294-298, 2002

451. Yang CW, Li C, Jung JY, et al: Preconditioning with erythropoietin protects against subsequent ischemia-reperfusion injury in rat kidney. FASEB J 17:1754-1755, 2003

452. Jindal KK, Hirsch DJ, Belitsky P, Whalen MA: Low-dose subcutaneous erythropoietin corrects the anaemia of renal transplant failure. Nephrol Dial Transplant 7:143-146, 1992

453. Muirhead N, Cattran DC, Zaltzman J, et al: Safety and efficacy of recombinant human erythropoietin in correcting the anemia of patients with chronic renal allograft dysfunction. J Am Soc Nephrol 5:1216-1222, 1994

454. Traindl O, Barnas U, Franz M, et al: Recombinant human erythropoietin in renal transplant recipients with renal anemia. Clin Transplant 8:45-48, 1994

455. Yoshimura N, Oka T, Ohmori Y, Aikawa I: Effects of recombinant human erythropoietin on the anemia of renal transplant recipients with chronic rejection. Transplantation 48:527-529, 1989

456. Becker BN, Becker YT, Leverson GE, Heisey DM: Erythropoietin therapy may retard progression in chronic renal transplant dysfunction. Nephrol Dial Transplant 17: 1667-1673, 2002

457. Lezaic V, Djukanovic L, Pavlovic-Kentera V: Recombinant human erythropoietin treatment of anemia in renal transplant patients. Ren Fail 17:705-714, 1995

458. Page B, Zingraff J: Resistance to rHuEpo and kidney graft rejection. Nephrol Dial Transplant 9:1696-1697, 1994

459. Gill JS, Abichandani R, Khan S, Kausz AT, Pereira BJ: Opportunities to improve the care of patients with kidney transplant failure. Kidney Int 61:2193-2200, 2002

460. Lopez-Gomez JM, Perez-Flores I, Jofre R, et al: Presence of a failed kidney transplant in patients who are on hemodialysis is associated with chronic inflammatory state and erythropoietin resistance. J Am Soc Nephrol 15:2494-2501, 2004

461. Atkins D, Best D, Briss PA, et al: Grading quality of evidence and strength of recommendations. BMJ 328:1490-1494, 2004

Supplement to

VOL 47, NO 5, SUPPL 3, MAY 2006

AJKD American Journal of Kidney Diseases

Vol 47, No 5, Suppl 3, May 2006 pp S1-S146

American Journal of Kidney Diseases

National Kidney Foundation™
KDOQI
KIDNEY DISEASE OUTCOMES QUALITY INITIATIVE

# KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease

The Official Journal of the National Kidney Foundation™

W.B. Saunders, an Imprint of Elsevier