

Contents

Introduction	1
Aim of the Work	3
Chronic Kidney Disease	
• Introduction	4
• Defining Chronic Kidney Disease And Developing A Staging System	4
• Risk Factors of Chronic Kidney Disease	7
• Detection of Individuals at Higher Risk of Developing Chronic Kidney Disease	7
• Diagnosis of Chronic Renal Failure	9
• Clinical Picture of CKD	9
• Detecting Kidney Damage	11
• Assessment of Renal Function	14
Anemia of Chronic Kidney Disease	
• Introduction	17
• Prevalence of Anemia In Chronic Kidney Disease	18
• Pathogenesis	20
• Inflammation and Anemia in Patients with Chronic Kidney Disease	23
• Malnutrition and Anemia in Patients with CKD	24
• Anemia and Cardiovascular Diseases in CKD	26
• Association Between Anemia And Left Ventricular Hypertrophy In Chronic Kidney Disease	27
• Post Transplantation Anemia	32
• Diagnosis of Anemia of Chronic Kidney Disease	35
• Defining the Optimal Target Haemoglobin Concentration for Chronic Kidney Disease Patients	37
Conventional Treatment for Anemia of Chronic Kidney Disease	
• Introduction	39
• Erythropoietin	39
• Recombinant Human Erythropoietin (Epoetin)	40
• History of Erythropoiesis Stimulating Agents (ESAs)	42

• Pharmacokinetic Differences	43
• Approved Indications And Dosing	43
• Extended Dosing Intervals	44
• Advantages of ESAs	45
• Mechanisms of Organ Protection by Erythropoiesis Stimulating Agents (ESAs)	48
• Advantage of Early Correction of Anemia in Patients With CKD	49
• Erythropoietin Use In Treatment of Anemia In Patients Receiving Peritoneal Dialysis	49
• Risks of Erythropoiesis Stimulating Agents (ESAs)	50
• Erythropoietin resistance	52
• Adjuvant Therapy in Patients Treated With rHuEpo	55
• IL-6 As A Therapeutic Target	56
• Iron Deficiency Anemia In Patients With CKD	57
• Physiology of Iron Metabolism	58
• Laboratory Assessment of Erythropoiesis and Iron Status	61
• Iron Deficiency and Estimation of Iron Status in Chronic Kidney Disease	65
• Iron therapy for treatment of anemia of CKD	66
• Risks of Iron Supplementation	71
• NKF-DOQI Clinical practice Guidelines	73
• Iron Support	73
• Dialysis-Related Carnitine Disorder and Levocarnitine Pharmacology	76

New Treatment for Anemia of Chronic Kidney Disease

• Introduction	83
• Darbepoetin Alfa	84
• Continuous Erythropoiesis Receptor Activator	85
• Synthetic Erythropoiesis Protein	90
• Erythropoietin Fusion Protein	93
• Erythropoietin-Mimetic Peptides	94
• GATA Inhibition	98
• Haemopoietic Cell Phosphatase Inhibitors	98
• Hypoxia Inducible Factor α Stabilisers	100

• Erythropoietin Gene Therapy	103
• New Approaches to Adjuvant Iron Therapy	104
• Pure Red Cell Aplasia	107
Summary	118
References	120

List of Tables

Items	Pages
Table 1. Staging System and Action Plan for Chronic Kidney Disease.	6
Table 2. Expressions of urinary protein concentration and their approximate equivalents and clinical correlates	12
Table 3. Prevalence of anemia by degree of renal dysfunction among CKD patients in different studies	18
Table 4. Regression of left ventricular hypertrophy, evaluated by changes in left ventricular mass index, after partial correction of anemia in CKD patients	31
Table 5. Pharmacokinetic Properties of Erythropoiesis-Stimulating Agents*	43
Table 6. Factors Associated with Erythropoietin Resistance in ESRD	54
Table 7. Laboratory assessment of iron status.	61
Table 8. Oral iron preparations.	67
Table 9. Available intravenous iron preparations .the 2 available iron dextran differ in molecular weight2 available.	68
Table 10. Novel agents for stimulating erythropoiesis	83
Table 11. Adverse effect of CERA compared with epoetin	90
Table 12. Pharmacokinetic profile of SEP and Epo in rats	92
Table 13. Treatment for PRCA.	114

List of Figures

Items	Pages
Figure 1. Serum immunoreactive erythropoietin and haemoglobin	20
Figure 2. Epo and erythropoiesis	21
Figure 3: Schematic representation of intracellular mechanism of action of Erythropoietin	41
Figure 4. Iron Balance	60
Figure 5. National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines	74
Figure 6. National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) guidelines	75
Figure 7. Mean (SE) predialysis plasma concentrations of L-carnitine during the first 12 months of hemodialysis in patients (n =21) with ESRD.	78
Figure 8: Comparison of epoetin and darbepoetin alfa	84
Figure 9: Comparison of epoetin and CERA	86
Figure 10: Mean half-lives of CERA, darbepoetin alfa, epoetin alfa, and epoetin beta	87
Figure 11: Haemopoietic activity of (SEP) and (EPO)	91
Figure 12: Diagrammatic representation of erythropoietin signalling, showing negative influence of HCP.	99
Figure 13: Mechanism of action of prolyl hydroxylase inhibitors	102
Figure 14. The rates of rhuEPO mediated PRCA	108