UNIVERSIDADE D
COIMBRA

Soraia Carolina Pedrosa de Paiva Fidalgo

Assessment of the Effect of Renal Impairment on Pharmacokinetics

Dissertação no âmbito do Mestrado em Biotecnologia Farmacêutica orientada pelo Professor Doutor Sérgio Paulo de Magalhães Simões e pelo Professor Doutor José Luís de Almeida e apresentada à Faculdade de Farmácia da Universidade de Coimbra.

Julho de 2019

Assessment of the Effect of Renal Impairment on the Pharmacokinetics

Soraia Carolina Pedrosa de Paiva Fidalgo

Dissertação de Mestrado na área científica de Biotecnologia Farmacêutica orientada pelo Senhor Professor Doutor Sérgio Paulo de Magalhães Simões e pelo Senhor Professor Doutor José Luís de Almeida apresentada à Faculdade de Farmácia da Universidade de Coimbra.

Julho de 2019

Try to leave this world a little better than you found it and, when your turn comes to die, you can die happy in feeling that at any rate you have not wasted your time but have done your best.

Robert Baden-Powell

Agradecimentos

Em primeiro lugar tenho de agradecer à minha mãe, ao meu pai e à minha irmã pelo apoio incondicional, pela força e por nunca deixarem de acreditar que eu seria capaz.

Aos meus amigos, àqueles que conheço desde sempre e aos que o destino me trouxe e que caminham a meu lado, com quem partilhei todas as preocupações, angústias, cansaço e vitórias sentidas de forma especialmente intensa nesta fase. Pelas palavras de encorajamento e por não me deixarem esquecer que *"depois da tempestade vem a bonança"*.

Aos colaboradores da BlueClinical, pela preocupação constante, pela motivação e por permitirem o meu desenvolvimento a nível profissional e pessoal. Ao Serafim, pelo estímulo, apoio, paciência e conhecimentos que me passou durante este percurso.

A todos, o meu grande OBRIGADA!

Soraia

Abstract

Chronic Kidney Disease and Acute Kidney Injury are a worldwide problem of public health and represent major kidney-related diseases that contribute to increased mortality and morbidity. The growth in the number of patients with kidney disease increases healthcare costs related to the detection, prevention and management of the disease and associated comorbidities to patients, families and health systems. Kidney impairment may affect the pharmacokinetics of a drug in each of its processes: absorption, distribution, metabolism or excretion in an unpredictable way. Moreover, there is insufficient evidence of the changes that occur in drugs pharmacokinetics in patients with chronic or acute kidney disease. Kidney diseases are very heterogeneous, varying in cause, severity and effects on the kidney structures. Each condition has different treatments and, therefore, different preferential approaches to optimize drug therapy. Designing optimal doses for renal impaired patients is still a challenge because it depends of an accurate characterization of pharmacokinetic parameters and on the assessment of kidney function. This fact challenges the development of standardized guidelines to properly adjust drug dosage. Failure to accurately adjust a dosing regimen can predispose the individual to both under- or over-dosing leading to lack of therapeutic effects or accumulation of parent drug and/or its metabolites that may lead to the occurrence of toxicity and adverse drug reactions. Appropriate dosing in renal impaired patients is needed to maximize therapeutic effect, minimize toxic effects and avoid unnecessary expenses to the patient and to healthcare systems. Due to lack of specific information on individual variability and disease heterogeneity, strategies to dosage adjustment should be analyzed in a case-by-case basis. Available information regarding treatment of patients with renal impairment is limited because conducting clinical trials in these patients is challenging and costly. Nowadays, there is an urgent need to fill the gaps to better personalize medicine and drug prescription to improve patient's life expectancy and quality of life.

Keywords: Kidney Disease; Renal Impairment; Chronic Kidney Disease (CKD); Acute Kidney Injury (AKI), Pharmacokinetics (PK); Dose Adjustment; Regulatory.

Resumo

A Doença Renal Crónica e a Doença Renal Aguda são um problema comum de saúde pública uma vez que são fatores de risco para doenças associadas que aumentam a morbilidade e mortalidade a nível mundial O aumento do número de doentes com doenças renais continua a aumentar, consequentemente, os custos de saúde associados à deteção, prevenção e gestão da doença e de complicações subsequentes, tanto ao doente como aos sistemas de saúde também aumentam. A insuficiência renal afeta, de forma imprevisível, a farmacocinética dos fármacos em todos os processos, absorção, distribuição, metabolismo e excreção. Não obstante, há falta de evidência das alterações na farmacocinética tanto em pacientes com doença renal crónica como em pacientes com doença renal aguda. As doenças renais são muito heterogéneas, variando na causa, gravidade e *outcomes* clínicos nas estruturas renais. Cada condição apresenta diferentes tratamentos e diferentes métodos de otimização de dose. O desenho de doses adequadas para doentes com insuficiência renal constitui um desafio clínico uma vez que depende de uma caracterização correta do perfil farmacocinético do fármaco e da avaliação da função renal. Isto torna difícil o desenvolvimento de *guidelines* padrão para a modificação correta da dose. Um ajuste de dose incorreto expõe o doente a doses sub- ou supra-terapêuticas e, consequente, à falta de resposta terapêutica ou à acumulação tóxica do fármaco e/ou de seus metabolitos e consequentes reações adversas. Um ajuste de dose adequado visa maximizar o efeito terapêutico, minimizar efeitos tóxicos e evitar custos desnecessários ao doente e aos sistemas de saúde. As estratégias de ajuste de dose devem ser analisadas caso-a-caso devido à falta de informação específica sobre a variabilidade individual e à heterogeneidade da doença. A informação disponível relativa ao tratamento de doentes com insuficiência renal é limitada uma vez que a condução de ensaios clínicos nestes doentes é trabalhosa e dispendiosa. Por forma a aumentar a esperança média e a qualidade de vida doente através da medicina personalizada e da prescrição adequada de fármacos, é necessário preencher as lacunas existentes nesta área.

Palavras-chave: Insuficiência Renal; Doença Renal Crónica; Doença Renal Aguda; Farmacocinética; Assuntos Regulamentares; Ajuste de Dose.

Table of Contents

Index of Tables

Index of Figures

Abbreviations

ADME	Absorption, Distribution, Metabolism, Excretion
AKI	Acute Kidney Injury
AUC	Area Under the Curve
CGA	Cause, GFR category, Albuminuria category
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Equation
Cl	Clearance
Cmax	Maximum Concentration
CNS	Central Nervous System
CYP450	Cytochrome P450
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
ESRD	End of Stage Renal Disease
F	Bioavailability
FDA	US Food and Drug Administration
fe	Fraction excreted unchanged
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
ISN	International Society of Nephrology
IV	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
MDRD	Modification of Diet in Renal Disease Equation
NS	Nephrotic Syndrome
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OAT	organic anionic transporters
OATP	organic anion transporting polypeptide
OCT	organic anionic transporters
P-gp	p-glycoprotein
RRT	Renal Replacement Therapy
SDG	Sustainable Development Goals

$t_{1/2}$	Elimination Half-life
Vd	Volume of Distribution
WHO	World Health Organization

1. Introduction

Jean Baptiste Podelin, recognized as Molière, was a French poet, actor and well-known playwriter of the 17th century. In 1673, Molière wrote his last work *La malade imaginaire*, a comedy-ballet about an old hypochondriac. In this work, Molière wrote "*Presque tous les hommes meurent de leurs remèdes, et non pas de leurs maladies",* which means, "Most people die from the remedy rather than from the illness". Even though this was said in the 17th century, it can be applied nowadays and should not be underestimated.

The kidneys are a major internal fluid regulatory organ of the body. Therefore, changes in the regulatory functions usually results in systemic complications and impaired pharmacology of many drugs. Kidney disease has been described as the most neglected non communicable chronic disease with indirect impact on global mortality and morbidity. (Luyckx, Tonelli e Stanifer, 2018) Besides impaired quality of life and reduced life expectancy, the economic impact of kidney disease is massive. Early diagnosis of the disease can reduce the overall costs and increase the efficacy of drug response. Patients with kidney diseases need special care about drug therapy because drugs can have lack of efficacy or lead to adverse effects. If drug dosage is not properly modified according to patients' conditions, complications related to improper prescription can be worse than the disease itself. Adequate prescription is not and can't be blindly standardized. There are guidelines from regulatory agencies and Kidney Disease: Improving Global Outcomes that aim to guide clinicians' decisions however, they can't replace clinicians' critical judgement, expertise and opinion.

Rising prevalence of chronic kidney disease or acute kidney injury increased the attention given to the diseases and the need for more accurate drug therapy and disease consciousness. The 17 Sustainable Development Goals (SDG) created and adopted by the United Nations aims at promoting dignity, peace, prosperity and protection for everyone and for the planet. Although only SDG number 3 targets directly to guarantee health and well-being for all ages, accomplishment of all of the 17 SDGs should provide impact in global and individual kidney health. (United Nations, [s.d.]) Improvement in nutrient and healthcare access, reduction of armed conflicts, adequate preparation for natural disasters, public health programs that aim to promote health communication and awareness of screening, diagnosis and preventive actions, improvement in partnerships for research and healthcare financing are actions related to the other SDGs rather than number 3 that are relevant to promote decreasing kidney diseases prevalence and to increase the ability to deliver kidney care. (Luyckx, Tonelli e Stanifer, 2018)

The purpose of this work is to give a wide-ranging assessment in kidney diseases, their impact in the pharmacokinetics of drugs as well as to provide a review of the strategies used to modify drug dosage and the regulatory framework to raise consciousness about the problem of adequate prescribing to patients with renal impairment.

2. Kidney Diseases Worldwide

Kidney disease is a global problem of public health. According to the International Society of Nephrology (ISN), 850 million people worldwide have any kind of kidney disease, from several causes. (Internation Society of Nephrology, [s.d.]) Chronic Kidney Disease (CKD) and Acute Kidney Disease (AKI) represent major kidney-related diseases that contribute to increased mortality. CKD kills ever year at least 2.4 million people while AKI affects 13 million people and causes the death to 1.7 million people, according to ISN data.

Burden of kidney diseases is increasing, which calls for better surveillance systems, as well as prevention and disease management strategies. (Crews *et al.*, 2019) It is difficult to know the exact burden of kidney diseases since there is inconsistent data collection and lack of surveillance practices globally. Taxonomy of kidney diseases doesn't help, as well. (Levey, Levin e Kellum, 2013)

As a consequence, surveillance data and collection systems are also not consistent across different disease stages. For that reason, global impact and importance of kidney disease is not fully established. World Health Organization (WHO) describes kidney diseases as the most neglected chronic disease with indirect impact on global morbidity and mortality because it is a risk factor for cardiovascular diseases, diabetes, hypertension and HIV. (Luyckx, Tonelli e Stanifer, 2018)

Kidney diseases have an enormous economic impact because many patients end up in renal replacement therapies, both dialysis and transplantation. Healthcare costs to detect and manage the disease and associated comorbidities are also vast and increase with disease progression. For that reason and because it is affected by age, social-economical, cultural, environmental and political factors, disease impact and kidney care vary across the world, even between developed countries. These differences are related to all range of kidney diseases – CKD, AKI, kidney diseases screening in high risk populations and prevention methods in hospitalized patients. (Crews *et al.*, 2019) According to the WHO report of "the top 10 causes of death", published in March 2018, in 2016, kidney diseases were the ninth cause of death in high-income countries. (World Health Organization, 2018)

The United States National Kidney Foundation founded The Kidney Disease Outcomes Quality Initiative (KDOQI) in 2002. KDOQI goal was to create a set of guidelines, after the one published about dialysis in 1997, related to all stages of kidney disease. Later, in 2012, this

mission was renamed "Kidney Diseases: Improving Global Outcomes" (KDIGO). KDIGO became an independent non-profit foundation that aimed to promote consciousness of kidney diseases with publication of Clinical Practice Guidelines regarding kidney diseases with valuable and practical recommendations given by nephrology experts. (Kidney Disease: Improving Global Outcomes, [s.d.])

Global awareness of the impact that kidney diseases and related comorbidities need to increase worldwide. According to the Kidney Global Health Atlas of 2019 written by the ISN, 12 opportunities were identified to reduce burden of kidney diseases and to improve kidney care: (International Society of Nephrology, 2019)

I. Develop and implement policies and strategies for kidney disease prevention and treatment.
II. Develop and implement strategies to prevent or reduce risk factors.
III. Implement and work with surveillance mechanisms and databases to assess burden of kidney disease.
IV. Promote education campaigns regarding kidney disease to high risk populations.
V. Promote awareness to healthcare providers and improve access to adequate tools and information.
VI. Support nephrologists.
VII. Improve access to effective and affordable kidney therapy to manage risk factors and further complications.
VIII. Implement early detection, prevention and treatment.
IX. Integrate early evidence-based treatment.
X. Promote equitable access to kidney care (dialysis, transplantation and support).
XI. Expand kidney transplantation programs.
XII. Support further investigation and translational research.

2.1. Chronic Kidney Disease

2.1.1. What is Chronic Kidney Disease?

Chronic Kidney Disease (CKD) is defined as progressive and irreversible abnormalities in kidney structure, leading to loss of functional nephrons and, consequently, kidney function, for longer than three months. CKD is a term used to describe a heterogeneous span of disorders that affect kidney structure and function at different levels of severity. (KDIGO, 2013) The kidney has high adaptability. Therefore, the remaining functional nephrons try to compensate the loss of renal activity. However, they usually end up losing their function, decreasing kidney function. (Gilbert, 2013)

Definition, classification and limits of CKD are established based on the estimated GFR and kidney damage (in signs as albuminuria, urinary sedimentation and structural abnormalities). GFR is the mostly used marker to assess renal function therefore, several equations have been developed to predict levels of glomerular filtration. These equations were previously addressed. Another method used for risk stratification is assessment of albuminuria. The most common and economic, although low accurate, method to estimate albumin excreted in urine is dipstick analysis, followed by 24-hour urine assessment. (Richard, J Johnson; John e Floege, 2014) Using these two methods, CKD definition came to be levels of albuminuria higher than 30 mg/day, GFR lower than 60 mL/min/1.73 m^3 and presence of structural damage in the kidneys and urinary tract. (Webster *et al.*, 2017)

KDIGO established a system for CKD staging, which remains an important step to clinical practice. It is referred as "CGA Staging", C for cause of the disease, G for GFR category and A for albuminuria category. Disease stratification is a guide for clinicians predict risk for complications, disease progression, aiming at a better management and monitoring of the disease, as well as taking decisions regarding treatment.

Table 1 - CGA Staging of CKD (by KDIGO, 2013)

CKD Stage	eGFR (ml/min)	Description
1	> 90	Kidney damage with normal or increased GFR
2	60 – 89	Kidney damage with slight decreased GFR
3	30 – 59	Moderate decrease in GFR
4	15 – 29	Severe decrease in GFR
5	< 15 or dialysis	Kidney failure - End of Stage Renal Disease (ESRD)

The most popular method for estimation of GFR is using serum creatinine. Creatinine is a low molecular weight end-product of muscle catabolism therefore, its levels are proportional to muscle mass in the body. Creatinine is a marker for renal clearance because it does not form complexes with plasma proteins being, therefore, easily filtered in the glomeruli with only a small part secreted in the tubules. Creatinine is freely filtered, it isn't metabolized in the kidney and isn't reabsorbed. Therefore, values of creatinine Clearance can be associated to GFR value. It is widely used as an endogenous filtration marker because it is easy to measure and there are several assays that can be used with low costs associated. Nevertheless, there is a number of conditions can affect serum creatinine concentrations independent from GFR: creatinine levels are decreased with age and in female gender due to lower or smaller muscle-mass and in malnutrition or muscle wasting conditions. On the other hand, creatinine levels are increased in situations where muscle gain is predominant or with high ingestion of cooked meats. In obese subjects, creatinine levels are not changed because creatinine formation is not promoted. (Richard, J Johnson; John e Floege, 2014) Since creatinine concentrations can change independent from GFR, additional methods, such as serum levels of cystatin C, are recommended as confirmatory test for research purposes. (KDIGO, 2013)

KDIGO guidelines focus on albuminuria rather than proteinuria because albumin is the main urinary protein component in kidney diseases. (Gilbert, 2013) Nevertheless, variability in albumin excretion and assessment due to diet, exercise and posture can mistake CKD staging. (Richard, J Johnson; John e Floege, 2014) Albuminuria is an abnormal loss of albumin by urine due to an increased in glomeruli permeability to large molecules. (KDIGO, 2013)

Table 2 - Albuminuria categories (by KDIGO, 2013)

Albuminuria categories		
A1	**A2**	**A3**
Normal to slightly increased	Moderately increased	Severely increased
< 30 mg/g	30 – 300 mg/g	> 300 mg/g

2.1.2. CKD Risk factors

Many risk factors are associated to the development of CKD. GFR decreases with aging, increasing, therefore, the risk to develop CKD. Women have increased risk to develop CKD

and lower risk for ESRD when compared to men. Ethnicity also influences the risk for CKD due not only to genetic variants but also to cultural and behavioral issues. (Genovese *et al.*, 2010) Socioeconomic factors also play a role in CKD incidence. Lower socioeconomic status increases the risk for disease development because there is limited access to adequate healthcare conditions. Comorbidities are the main cause and risk factor to develop CKD. The main causes are diabetes and hypertension, but any conditions that is a risk factor to cardiovascular disease is also a risk factor to kidney disease. The link between heart and kidney is strong. (Robles-Osorio e Sabath, 2016) Episodes of kidney injury, either AKI or systemic diseases, of which diabetic nephropathy is the most frequent, also increase the chance to develop CKD. CKD is a risk factor for AKI and episodes of AKI increases the risk for CKD progression. (Gilbert, 2013) Nephrotoxic drugs can also lead to CKD development. Non-steroidal anti-inflammatories, aminoglycosides or lithium are examples of drugs that can contribute to CKD with chronic use. (Richard, J Johnson; John e Floege, 2014)

According to KDIGO Guidelines, prognosis of CKD (expressed as risk of morbidity and mortality) is defined by albuminuria, GFR categories and CKD cause. A system of four colors was created and combined with albuminuria and GFR categories. Prognosis of CKD can be predicted as low (green), moderately increased (yellow), high (orange) or very high risk (red). (KDIGO, 2013) Prognosis will vary depending on GFR, albuminuria levels and other comorbidities therefore, to develop an adequate prediction, these factors must be considered.

Table 3 - Prognosis of CKD (adapted from Gilbert, 2013)

		Albuminuria Categories		
		A1	A2	A3
GFR Categories	G1	Low	Moderately increased	High
	G2	Low	Moderately increased	High
	G3a	Moderately increased	High	Very high
	G3b	High	Very high	Very high
	G4	Very high	Very high	Very high
	G5	Very high	Very high	Very high

2.1.3. CKD Progression

KDIGO created a conceptual model for CKD which describes the natural history of the disease, starting with previous conditions associated with increased risk for development of kidney disease, followed by CKD stages and ultimately ending in the need for renal replacement therapy. During the whole span of the disease, there are associated complications, namely drug toxicity, metabolic disorders, cardiovascular diseases, infections and cognitive impairment, among many others. (KDIGO, 2013)

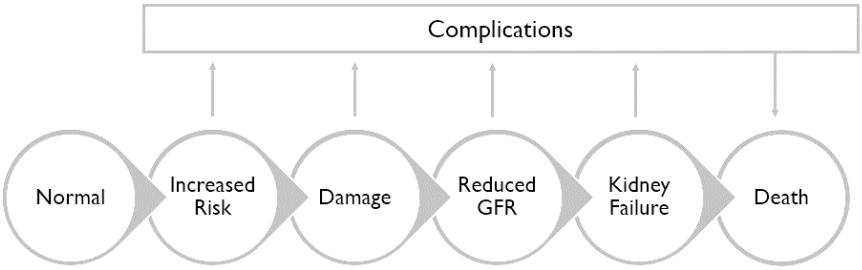

Figure 1 - Conceptual model for CKD (adapted from Gilbert, 2013)

The natural course of the disease relies in the deterioration of the kidney structure and in the decrease of GFR. Rate of progression of CKD is variable and not all patients with CKD progresses and develop End of Stage Renal Disease (ESRD). (Gilbert, 2013) Management of the disease in earlier stages can delay the progression of disease to later stages and, if action is taken early, kidney function deterioration can be reversible. (Richard, J Johnson; John e Floege, 2014)

CKD is asymptomatic until later stages, such as G4 or G5. Symptoms are unspecific and must be specifically sought to properly associate them to CKD because patients adapt to them due to their slow evolution. (Richard, J Johnson; John e Floege, 2014) At stage G1, patients usually have no symptoms. Kidneys are properly functioning and apparently healthy, sometimes showing only indirect signs of kidney damage like albuminuria. Sometimes there are also structural changes, only detectable by kidney biopsy. In G2, kidneys are functioning however with minor damage with signs of albuminuria. In G3, the kidneys have more damage and are not working well. This stage has been divided in G3a and G3b according to GFR levels. Patients with stage 3 CKD can develop symptoms like swelling, back pain and over-urinating, often confused with the clinical picture of the disease that is causing the kidney injury. Moreover, anemia, bone disease and high blood pressure can also be present. In G4, kidneys are

significatively damaged and management to avoid or prepare to kidney replacement must be considered. In CKD stage 5, kidneys have lost their function. This stage is commonly called End of Stage Renal Disease (ESRD). Patients are symptomatic and may express itching, muscle cramps, nausea and vomiting, respiratory and sleep disorders. Since kidneys can no longer eliminate toxic substances, dialysis or kidney transplant must be considered. (American Kidney Fund, [s.d.]) Patients in stage 5 of CKD require Renal Replacement Therapy (RRT) as a supportive method for removing drugs and metabolites from the systemic circulation. Delaying start of RRT can lead to an increase risk for mortality however, although there is no right time based on GFR levels measure to start dialysis. (Richard, J Johnson; John e Floege, 2014)

Dialysis is a non-natural mechanism in which metabolites, drugs and toxic substances that, in healthy circumstances would be eliminated by the kidney, are removed from bloodstream to the dialysis fluid without disturbing the electrolyte equilibrium of the organism. Blood passes through a membrane that retains drugs or toxins that needed to be eliminated. In hemodialysis, it is an extra-corporeal membrane, the dialyzer. In Peritoneal Dialysis, that membrane is the peritoneum. Both methods aim to remove drugs and toxic substances from the body to prevent accumulation and adverse effects. These methods are not addressed in this work. (Hon, 2017)

2.1.4. CKD Complications

Several adverse complications arise from CKD. They tend to appear with disease progression and GFR decline.

Anemia is common in patients in G3 to G5 stage of CKD and it is primarily caused by a decline in erythropoietin synthesis and aggravated by low levels of iron, as well as chronic inflammation. Anemia can increase the risk for cardiovascular and neurologic complications and further aggravate kidney damage.

Cardiovascular disorders (acute coronary syndrome, stroke, heart failure and sudden cardiac death) are a major complication related to CKD caused by decreased capillary density, increased myocardial fibrosis, albuminuria and abnormal coagulation. (KDIGO, 2013) Most patients with CKD die due to cardiovascular complications rather than the kidney disease itself. (Thompson *et al.*, 2015)

Bone and mineral disorders are also associated to CKD. Hyperphosphatemia aggravates and promotes hyperparathyroidism and therefore, the development of renal bone disease. Simultaneously, lack of vitamin D production leads primarily to hypocalcemia, both lead to hyperparathyroidism. Atypical serum concentrations of calcium, phosphate and magnesium can lead to a complex bone disorder called renal osteodystrophy (bone disease caused by CKD) and can be expressed by an abnormal osteoclast and osteoblast activity, leading to osteomalacia and osteoporosis. (Richard, J Johnson; John e Floege, 2014)

Infection is a common CKD complication and the second most common cause of death. (Richard, J Johnson; John e Floege, 2014) Patients with CKD have alterations in their immune system leading to bacterial, viral infections or chronic inflammation. Vaccination and treatment for inflammation are affected by kidney diseases thus dosage adjustment is needed.

Uremic encephalopathy is a neurologic disorder that can appear in CKD patients. It is due to the lower metabolic activity and oxygen feasting of the brain, and it is not correlated to the level of renal dysfunction. (Richard, J Johnson; John e Floege, 2014) Uremic encephalopathy can be clinically expressed as mental (mood changes, impaired concentration and cognition, insomnia, illusion, coma) or motor (tremor, hyperreflexia, seizures) changes.

Gastrointestinal (GI) complications can alter bioavailability of drugs increasing, therefore, difficulty of drug response. Esophagitis, peptic ulcers, gastritis, delayed gastric emptying or gastroparesis are among the most frequent GI complications.

2.1.5. CKD Management

Management of CKD is based on the risk for progression. Greater risk is associated with increased management intensity and cumulative therapy. (Gilbert, 2013) Treatment is recommended for each albuminuria and GFR category based on cause of the disease, albuminuria or GFR level and associated diseases. Cumulative therapy is recommended, which means that treatment for a certain disease stage includes care for previous stages. Patients with an albuminuria category higher than and including A2 combined with a GFR category higher than and including G3a (high or very high risk), are recommended to have cumulative treatment for management of both albuminuria and low GFR. (Gilbert, 2013) CKD management includes identifying diagnosis, reducing disease progression and the risk for comorbidities caused by renal dysfunction. (KDIGO, 2013)

2.2. Acute Kidney Injury

2.2.1. What is Acute Kidney Injury?

Acute Kidney Injury (AKI) is defined as an abrupt decline in GFR that leads to accumulation of nitrogenous substances that would be eliminated by the kidneys with changes in kidney structure and function. (Richard, J Johnson; John e Floege, 2014) (Gilbert, 2013) (KDIGO, 2012) The term Acute Kidney Injury englobes an ample range of conditions, since minor changes in kidney function until clinically significant changes requiring RRT.(Makris e Spanou, 2016) (KDIGO, 2012) Definition and classification AKI is based on the underlying condition that caused kidney injury and on increases of serum creatinine levels over a period. According to KDIGO guidelines, AKI is defined as an increase in serum creatinine levels of 0.3 mg/dl or more in 48 hours of patient observation, an increase in serum creatinine of 1.5 times or more baseline in a period of 7 days or a decrease in urine volume below to 0.5 ml/kg/h for a period of 6 hours. (KDIGO, 2012) (Richard, J Johnson; John e Floege, 2014) AKI can develop in consequence of several heterogeneous conditions that culminate with a decline in GFR. Although AKI is prevalent worldwide, the profile of patients varies from continent to continent. Common causes of AKI in less developed countries are more related to dehydration and infections and patients are younger, while in more developed countries, it usually occurs in hospitalized patients, mostly in surgical, pediatric or oncology areas, patient are older and with more comorbidities. (KDIGO, 2012)

In 2012, KDIGO established that AKI can be staged into three different levels based on severity of the disease. Each stage can be assessed by serum creatinine levels and urine output. Higher stages are related to increased severity and hospital mortality, longer hospitalization and increased healthcare costs. (Richard, J Johnson; John e Floege, 2014) (KDIGO, 2012) Patients that resist to AKI are at increased risk to develop CKD.

Table 4 - AKI staging (by KDIGO, 2012)

	Stage		
	1	2	3
Serum Creatinine (mg/dl)	1.5 – 1.9 times baseline Increase > to 0.3	2 – 2.9 times baseline	3 times baseline Increase > to 4
Urine output (ml/kg/h)	<0.5 for 6-12 hours	<0.5 for 12 hours or more	<0.3 for 24 hours or more Anuria for 12 hours or more

2.2.2. AKI Risk Factors

The kidneys can tolerate exposure to several factors without suffering damage due to their auto-regulation mechanisms and renal reserve. (Thomas, Coles e Williams, 1994) For this reason, there aren't specific risk factors to the development of AKI and, when damage is detected, it frequently indicates poor prognosis and systemic instability. (Richard, J Johnson; John e Floege, 2014) Therefore, recognition of these factors is the first step to reduce mortality and morbidity associated because there is no specific treatment to reverse the disease condition. Better outcomes with less complications and adequate therapy can be achieved if patients at risk to develop AKI are identified by clinicians. Risk to develop AKI increases with continuous exposure to factors that cause AKI or presence of factors that increase predisposition to AKI. Examples of exposure are underlying conditions like hemodynamic instability, sepsis, shock, burns, trauma, surgery (mostly cardiovascular surgery), nephrotoxic drugs or radiocontrast agents. After exposure, individuals respond differently due to susceptibilities factors that diverge from patient to patient. Susceptibility factors are, among others, dehydration, aging, female gender, pre-existing CKD, heart, lung or liver disorders, diabetes, cancer or anemia. (KDIGO, 2012)

There are four levels for risk assessment. Before and after exposure, after development of AKI and before complications. (KDIGO, 2012) Risk assessment before exposure aims to stratify patients that will undergo through therapies with potential to induce kidney damage. Risk assessment after exposure aims to control further risk factors resultant from initial exposure. At this level, patient vital signs, genetics and inflammatory response can be evaluated. After development of AKI, the purpose is to determine prognostic criteria to predict and consequently, prevent adverse clinical outcomes. The last level aims to maintain a regular patient follow-up to detect if the patient developed CKD, ESRD or cardiovascular events. (KDIGO, 2012)

AKI is more frequent in older patients than in younger patients due to structural and functional changes in kidneys and some comorbidities (like hypertension, diabetes or vascular diseases) that lead to reduced kidney capacity and GFR. Proteinuria and hyperuricemia are also risk factors for AKI as so pre-existing conditions with reduced GFR, namely in patients that went through surgery or radiocontrast. (Richard, J Johnson; John e Floege, 2014) (KDIGO, 2012)

2.2.3. AKI Causes

Medical history and examination of the patient with AKI give information about the original cause of AKI, prognosis and further complications. Important information that needs to be collected is related to previous procedures, systemic conditions, fluid loss, infections and, if adequate, immunosuppressive therapies. Causes of AKI are classically classified in prerenal, renal or postrenal. (Richard, J Johnson; John e Floege, 2014)

Pre-renal AKI situations are characterized by a decreased in kidney perfusion that may be caused by hypotension, hemorrhage, heart failure or cirrhosis. (KDIGO, 2012) Sepsis, hypovolemia and administration of vasoconstricting drugs like anti-hypertensive drugs or some antibiotics lead to a decrease in the glomerular filtration rate. Prerenal causes are not always benign and reversible however, renal failure and death are possible outcomes. The prognosis depends, not only on the renal reserve, but also on the severity and duration of the insult.

In Renal AKI, also called intra-renal or intrinsic, decline in GFR is directly associated to kidney damage and not to decreased perfusion or increased pressures. It can be a consequence of damage in one of the various components (vascular, glomeruli, tubules and interstitial). Common causes of renal AKI include acute glomerulonephritis, vasculitis, interstitial nephritis or, the most common cause of hospital-acquired AKI, acute tubular necrosis. Acute tubular necrosis may be caused by a toxic or ischemic insult to the kidneys. (KDIGO, 2012) Some patients are especially susceptible: patients who suffer from trauma, cardiovascular surgery, severe burns, pancreatitis, sepsis or chronic liver disease. (Richard, J Johnson; John e Floege, 2014)

Postrenal AKI is characterized by urinary tract obstruction. Obstruction increases intratubular pressure which leads to a dysfunction of the nephrons and decrease in GFR. Postrenal AKI may be reversible through intervention and patients can recover completely their renal function. However, if duration of obstruction is long enough, permanent damage in extrarenal system due to inflammation of fibrosis can occur.

2.2.4. AKI Progression

AKI is usually asymptomatic but sometimes can be expressed as lower urine production, swelling, fasting, nausea, vomiting or other neurological signs like confusion, anxiety or sleep alterations. (International Society of Nephrology, [s.d.])

KDIGO also created a conceptual model of AKI, similar to the one proposed to CKD. It represents the likely antecedents (risk factors) of AKI, progression of the disease, outcomes and the respective biomarkers for each disease phase. (KDIGO, 2012)

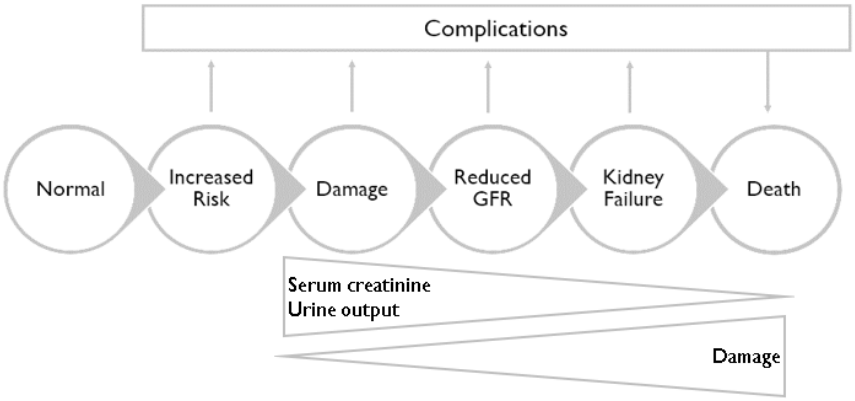

Figure 2 - Conceptual model for AKI (adapted from KDIGO, 2012)

Between each level of severity, a different plan of risk assessment, primary and secondary prevention and therapy should be followed. From early levels, when a risk assessment with early detection biomarkers is the priority, to more severe stages, when therapy and action plans to manage the causing disease are needed to reduce further complications and death. Each stage should call for a different approach. (Richard, J Johnson; John e Floege, 2014)

2.2.5. AKI Complications

AKI complications can aggravate kidney injury and increase mortality or hospitalization. Therefore, management of AKI complications is also important to improve therapeutic response and adequate treatment to prevent exacerbation of kidney injury.

Clinical complications associated to AKI are hyperkalemia, volume excess, acidosis, neurological disorders ranging from encephalopathy or neuropathy to coma, thrombocytopathy, anemia, myopathy, pleural effusion or chronic kidney disease. Prolonging AKI leads to multiple organ failure and death. (KDIGO, 2012)

2.2.6. AKI Management

Since specific treatment for AKI is not available, management of AKI must focus on premature recognition of changes in urine output and serum creatinine concentration levels to design adequate interventions and prevent complications and exacerbation of kidney damage.

Staged-based AKI management is the adequate approach to manage the disease according to the patient's susceptibilities and risk exposure to individualize clinical monitoring. According to KDIGO, as shown in Table 5, some action plans are appropriate at all disease stages while others are stage-specific. Discontinuation of nephrotoxic drugs, maintenance of volume status, hemodynamic monitoring, control of serum creatinine and urine output, prevention of hyperglycemia and avoidance of radiocontrast procedures are examples of management plans transversal to all AKI stages however, need for action increase with disease severity. (KDIGO, 2012) The diagnostic workup in patients with AKI depends on the clinical context, disease stage and disease duration. Moreover, drug dose adjustment, renal replacement therapy and eventual hospital admission are plans recommended for severe cases of AKI. AKI management plans according to each stage are expressed in Table 5.

Table 5 - AKI management action plans (adapted from KDIGO, 2012)

AKI Stages			
High Risk	1	2	3
Discontinuation of nephrotoxic drugs			
Maintain volume status and adequate perfusion			
Hemodynamic monitoring			
Monitor serum creatinine levels and urine output			
Avoid hyperglycemia			
Avoid radiocontrast procedures			
	Non-invasive diagnostic examination		
		Dosage adjustment	
		Renal Replacement Therapy	
		Intensive Care Unit admission	
			Invasive diagnostic examination

Identification of the underlying cause and maintenance of hemodynamic and fluid stability are important to promote rapid recovery of kidney function and to avoid volume excess. (Gilbert, 2013)

Supportive care in patients with AKI involves optimizing fluid volume and hemodynamic status, maintenance of electrolyte and acid-base balance and glucose control. (Gilbert, 2013) (Richard, J Johnson; John e Floege, 2014) The detailed description of these treatments falls out of the scope of this text.

After hospital discharge, patients with AKI are at an increased risk to develop CKD or ESRD. Therefore, long term follow-up of AKI survivors is essential to, if needed, start CKD management at earlier stages.

2.3. Nephrotic Syndrome

2.3.1. What is Nephrotic Syndrome?

Glomerular diseases often lead to kidney dysfunction. They can express by five clinical syndromes: nephrotic syndrome (NS), acute nephritic syndrome, chronic glomerulonephritis, rapidly progressing glomerulonephritis and asymptomatic urinary, abnormalities. These syndromes can be primary (their origin is in the kidney) or secondary to systemic diseases. (Gilbert, 2013) Recognition of each syndrome is made by symptoms, signs and urine and blood tests.

Nephrotic syndrome is characterized by peripheral edema, severe proteinuria with levels higher than 3.5 g/day/m^2, hypoalbuminemia with levels lower than 3.5 g/dl, lipiduria and in some cases, hyperlipidemia. NS has extensive metabolic impact that can influence overall health and different organs of the patient. (KDIGO, 2012) (Richard, J Johnson; John e Floege, 2014)

The proportion of albumin to higher molecular weight proteins loss by the glomerulus is called selectivity, being an indirect marker of the degree of damage of the glomerulus membrane. (Tencer, Bakoush e Torffvit, 2000) The smaller this proportion, the bigger the damage. It has prognostic value. (Lagrue *et al.*, 1991)

2.3.2. Nephrotic Syndrome Causes

Nephrotic Syndrome can be classified as primary, when it is confined to the kidney, or secondary, when it is a part of a broader disease with more other organ repercussion. Systemic conditions such as type 2 diabetes mellitus, systematic lupus erythematosus or amyloidosis are

common causes of NS. Other secondary causes of NS are immunologic, neoplastic, infection or allergic diseases, genetic syndromes or drug use. (Kodner, 2016) (Gilbert, 2013).

Age and ethnicity are useful for the differential diagnosis: in childhood, minimal change disease is the most frequent cause for NS while prevalence in adults, membranous nephropathy and focal and segmental sclerosis are prevalent.

2.3.3. Nephrotic Syndrome Progression

Diagnosis of NS is based on the five features that are characteristic of the disease: edema, proteinuria, hypoalbuminemia, hyperlipidemia and lipiduria. (Kodner, 2016)

Presence of peripheral edema is due to an extravasation of fluid from the intravascular to the interstitial space caused by low oncotic pressure related to hypoalbuminemia and hypoproteinemia. (Siddall e Radhakrishnan, 2012) Edema is the most common symptom of NS and often the only one. Depending on the severity of the disease, edema may be extended to the abdomen or genitalia in severe cases. In severe NS, intestinal wall edema affects drug absorption, reducing drug bioavailability. (KDIGO, 2012)

Proteinuria is generally asymptomatic and detected by urine dipstick or measured by 24-hour protein excretion however, if severe proteinuria is present, urine color may be different, sometimes presenting with foam. (Gilbert, 2013) Lipiduria is usually a result of proteinuria and is characterized by a deposit of lipid in cellular debris and casts. Hypoalbuminemia is an important consequence of proteinuria. Due to high protein losses, the liver increases albumin synthesis however, production is insufficient to compensate protein excretion leading to a decrease in albumin serum concentrations. Protein synthesis is not selective which means that other protein concentration levels rather than albumin may increase in nephrotic syndrome. (Richard, J Johnson; John e Floege, 2014)

Variations in plasma proteins are the main cause of high lipid levels. Increased hepatic synthesis and secretion of High Density Lipoprotein increases serum levels of both Low and High Density Lipoprotein. (Richard, J Johnson; John e Floege, 2014)

Mechanism of nephrotic syndrome is described in Figure 3.

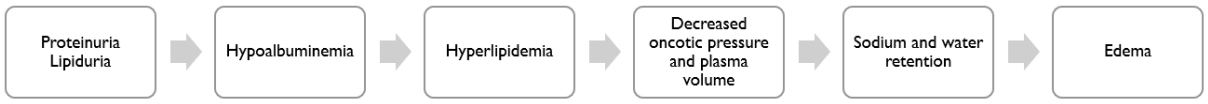

Figure 3 - Mechanism of nephrotic syndrome (adapted from Richard, J Johnson; John e Floege, 2014)

2.3.4. Nephrotic Syndrome Complications

Numerous systematic complications are associated with Nephrotic Syndrome. Complications are usually due to hepatic overproduction of proteins and elevated loss of proteins in urine. Complications of the underlying disease are also a part of the clinical picture. (Kodner, 2016)

NS is considered a wasting syndrome since the patient experiences muscle and fat loss. Nitrogen balance, defined as the difference between nitrogen ingested in diet protein and nitrogen excreted from the body, is often negative. High intake of protein, as well as administration of albumin, does not improve serum levels, because it increases protein loss in urine. (Richard, J Johnson; John e Floege, 2014)

Coagulation abnormalities expressed as thromboembolisms are frequent due to altered serum levels of coagulation proteins and hyperviscosity of the blood. Both venous and arterial thrombosis can occur however, venous thrombosis is more common. Frequency of venous thromboembolic events increase with decline of serum albumin. On the other hand, increased hepatic synthesis raises serum levels of coagulation proteins such as fibrinogen, protein C or factors V and VII leading to both arterial thrombosis and venous thromboembolism. Increased platelet aggregation and patient immobility also increases the risk for both coagulation irregularities. Hyperlipidemia can also contribute to accelerated atherogenesis resulting in arterial thrombosis. (Richard, J Johnson; John e Floege, 2014)

Patients with NS can also develop bacterial infections. Bacteria grow easily in areas with large fluid accumulation and edema and, due to increased protein excretion, humoral immune response is delayed. (Richard, J Johnson; John e Floege, 2014)

2.3.5. Nephrotic Syndrome Management

There is no specific treatment for nephrotic syndrome. Treatment for NS involves treating the underlying cause of the syndrome, addressing possible complications and features of the disease, namely preventing cardiovascular and infectious ones.

Patients with NS cannot be treated with diuretics to manage edema because patients are resistant and therefore lack of therapeutic response is observed. Moreover, loop diuretics also have lack of efficacy because they need to bind to proteins to be effective and serum protein levels are decreased in nephrotic syndrome. (Kodner, 2016)

Decreasing proteinuria is important since it leads to the development of several NS metabolic complications and patient's symptoms. Anti-proteinuric agents commonly used are inhibitors of angiotensin-converting enzyme or angiotensin receptor blockers. (KDIGO, 2012)

Treatment of hyperlipidemia is managed by careful administration of statins.

Anticoagulants as treatment for coagulation abnormalities and venous thrombosis are not usually considered in patients with kidney diseases due to the elevated risk of bleeding. However, in cases where benefits overcome the risk, low-molecular-weight heparin or warfarin can be used. (KDIGO, 2012) The decision to treat with anticoagulants or not should be taken by an individual approach. (Kodner, 2016)

The use of corticosteroids in managing nephrotic syndrome is frequent. (Kodner, 2016) In some cases it is the gold standard as, for example, in Minimal Changes Disease and Lupic Nephropathy. In other cases, the decision is guided by kidney biopsy, which also is very important for prognostication.

3. Pharmacokinetics in Renal Impairment

Pharmacokinetics (PK) is the term used to describe the study of a set of mechanisms performed by the body on a drug. They are commonly referred to as "ADME": A stands for absorption, D for distribution, M for metabolism and E for excretion. It aims to determine the onset, intensity and the duration of the drugs' actions in the body and to quantify the behavior of a drug through accurate determinations of the concentration in the blood. (Lamattina e Golan, 2009) The success of a drug therapy depends not only on the choice of it but also on the dose regimen that is elected. An understanding of pharmacokinetics allows health-care professionals to increase the efficacy and patient compliance and decrease the toxicity of the drug. Clinical pharmacokinetics deals with the application of pharmacokinetic principles to individual patients in order to effectively manage drug therapy. It includes components of therapeutic drug monitoring concerning therapeutic index of a drug – range of concentrations between the minimum effective concentration and minimum toxic concentration, with maximal effectiveness and insignificant adverse effects, and intra-individual factors such as drug interactions, adverse reactions and enzymes levels. The goal of pharmacokinetics is to achieve the optimal dose to be administrated and optimizing the dosing regimen to obtain the desired drug concentration in the body and reach maximal efficacy.

Kidney impairment may affect the PK of a drug in each of its processes, absorption, distribution, metabolism or excretion. The impact can be due to changes in any of the kidney's function – filtration, reabsorption and secretion, or due indirect impact in other organs of the gastrointestinal tract. Whether kidney impairment is chronic or acute, each situation drives different approaches to optimize treatment regimens. Failure to properly adjust a dosing regimen can predispose the individual to adverse drug reactions. (Lea-henry *et al.*, 2018) Several mathematical formulas have been used to measure pharmacokinetic parameters and define a concentration curve over time (AUC) for each drug in order to characterize the drug profile.

3.1. Absorption

Absorption represents the movement of a drug from the site of administration to the systemic circulation and the extent to which it occurs leads to its bioavailability. (Gonzalez, Coughtrie

e Tukey, 2010) Bioavailability (F) represents the fraction of drug absorbed that reaches the systemic circulation and escapes first-pass metabolism. (Gonzalez, Coughtrie e Tukey, 2010)

The extension of absorption depends on the route of administration, the physicochemical characteristics of the drug (size, lipid solubility) and intra-individual factors.

Bioavailability of drugs has critical implications since it is the major factor determining the drug dosage for different routes of administration. (Lamattina e Golan, 2009) It is determined by comparing plasma concentration data of a drug administrated orally (AUC oral) with plasma concentration data after intravenous (IV) administration (when the drug is immediately at the systemic circulation, AUC IV).

(1) Bioavailability (F) (Lamattina e Golan, 2009)

$$F = \frac{AUC\ oral\ \times Dose\ IV}{AUC\ IV\ \times Dose\ oral}$$

For solid drugs, the first required process is the disintegration and dissolution of the formulation to release the drug. This inactivates a portion of the drug before it enters the systemic circulation and is distributed to the site of action.

3.1.1. Routes of administration

Oral administration is the most common route of administration for its safety and convenience. (Gonzalez, Coughtrie e Tukey, 2010) However, it brings major problems like patient compliance, variability of absorption patterns and susceptibility to intra-individual characteristics or drug dissolution. Tablets, capsules or syrups may pass through first-pass metabolism, different pH environments, gastrointestinal secretions, degrading enzymes and a diversity of aspects that are individual dependent, affecting the bioavailability of the drug. Drug structure and physicochemical characteristics are also major aspects that affect the quantity of drug that reaches the systemic circulation. Lipid-soluble drugs are more absorbed from the gut while polar acids and bases tend to be slowly absorbed and rapidly eliminated in the faeces.

Parenteral administration includes IV, subcutaneous, intramuscular and intrathecal administration. Drugs administrated by IV route are immediately available in the systemic

circulation (bioavailability is 100%), decreasing the time that the drug needs to reach its target and, therefore, the onset of action of the drug. This brings a major advantage for emergency situations: the effect can be instantaneous. However, it increases the risk for adverse effects and overdosage. For subcutaneous and intramuscular administration, absorption occurs by simple diffusion. The extent of absorption is limited by circulation, by the capillary membranes and by the physicochemical characteristics of the drug. Generally, blood-brain barrier offers great protection to the brain. Yet, if the target organ is the brain, other routes of administration must be considered because several drugs may not be able to pass through the barrier. Numerous drugs that act on the Central Nervous System (CNS) may be administrated by an injection into the cerebrospinal fluid to guarantee that the drug reaches the intended target. Topical administration is mainly used for local effects. It involves absorption through mucous membranes which occurs readily. (Gonzalez, Coughtrie e Tukey, 2010) Depending on their physicochemical characteristics, some drugs can be administrated by inhalation. The lungs are a good site for absorption with rapid access to the systemic circulation due to their large surface area and extensive blood flow. Drugs can avoid first-pass metabolism and they can be absorbed more instantly nevertheless, allergies and systemic reactions are more frequent. Drug administration by inhalation is restricted to volatile and gaseous drugs or drugs that can be atomized to droplets for administration via aerosol. FDA recognizes 118 routes of administration. (U.S. Food and Drug Administration, 2018)

3.1.2. Absorption and renal impairment

There is incomplete data about the changes that occur in drug absorption in renal impaired patients. Oral administration is the route most affected by renal impairment as far as absorption is concerned. Other routes of administration like parenteral injection, topical or inhalation are less affected by renal impairment.

Gastrointestinal (GI) disorders are common in renal impaired patients which can lead to impaired drug absorption. (Shirazian e Radhakrishnan, 2010) In patients with Chronic Kidney Disease (CKD), it is often to observe pathophysiological changes in the gastrointestinal tract that can negatively affect drug absorption. (Nolin, 2015) Gastric pH can be increased due to the transformation of urea concentrations to gastric urease, gastric emptying can be reduced and there can also be edema of the digestive tract wall. (Shirazian e Radhakrishnan, 2010) Causes to the decreased gastric emptying are the concomitant administration of antiacids

containing aluminium to treat gastrointestinal symptoms and peritonitis (in the peritoneal dialysis patients). This impaired absorption of drugs leads to an increased time to reach maximum plasma concentration and possibly decreased maximum plasma concentration of the administrated drug. (Lam *et al.*, 1997) These patterns of changes, however, can't be applied to all drugs and are poorly quantified. Increase in pH may increase the bioavailability of weak acids.

In Acute Kidney Injury (AKI), absorption is poorly measured and may decrease, especially if there is edema of the GI wall, while in CKD absorption may decrease or increase. (Roberts *et al.*, 2018) It is possible that drugs that go through first-pass metabolism can exhibit increased bioavailability due to malfunction of metabolizing enzymes. (Atkinson, 1999)

Also, these patients are often polymedicated, which can lead to drug-drug interactions and possibly influence the absorption of other concomitant drug. (Verbeeck e Musuamba, 2009)

Usually, oral bioavailability is not measured in pharmacokinetic studies because other parameters are determined such as, clearance, volume of distribution and plasma half-life. Moreover, changes in the AUC after oral administration may not only be due to altered extension of absorption. (Verbeeck e Musuamba, 2009)

3.2. Distribution

After drug absorption, drug reaches the systemic circulation. The next process, drug distribution, is defined as the movement of the drug between systemic circulation and extravascular tissues. (Gonzalez, Coughtrie e Tukey, 2010) Concentration gradient forces the drug to pass to the interstitial fluid and then, to the tissues or organs until it reaches the target organ.

At the cellular level, there are several mechanisms that facilitate the passage of drugs from bloodstream to tissues, either passive or involving active mechanisms: (Lamattina e Golan, 2009)

- Passive Diffusion;
- Active transport;
- Facilitated diffusion.

When a drug is lipid-soluble and has small dimensions, it can cross the lipid bilayer according to a concentration or electric gradient without the help of membrane components. This process is called passive diffusion and it is the dominant process. Another type of transport across the membrane is active transport. It plays an important role for its capacity. In this type of transport, molecules cross the membrane against a concentration or electric gradient, requiring energy expenditure. As a consequence, the transported molecules will further increase the concentration or electric gradient and will then act as vehicles for drugs or other compounds. A third process of transmembranous transport is facilitated diffusion, which also requires a vehicle although it doesn't need energy expenditure. These mechanisms may all be very selective because they require a special molecular conformation of the transported molecule to fit in the transporter. This is important because they may also act as barrier to toxic substances.

Rate of distribution depends on the target organ, cardiac rhythm, blood flow, capillary permeability, physicochemical characteristics of the drug and binding of drug to plasma proteins. Many drugs have affinity for protein sites resulting in reversible binding and establishment of drug-protein complexes. (Gonzalez, Coughtrie e Tukey, 2010) Albumin and α_1-acid glycoprotein are the most common plasma proteins that bind to drugs. Albumin binds to acidic or steroidal drugs while α_1-acid glycoprotein binds mostly to basic or neutral drugs. Protein-drug interaction is fast, reversible, saturable and competitive since different ligands compete for the same protein site. Complexes lower the fraction of free drug in the blood decreasing, therefore, the fraction of drug able to bind to the target which might not be enough to produce therapeutic effect.

3.2.1. Volume of distribution

Volume of distribution (Vd) is the theoretical volume that would be necessary to contain the total amount of an administered drug at the same concentration that it is observed in the blood plasma. (Faculté de biologie et de médicine Université de Lausanne, [s.d.])

It refers to an apparent volume and is characteristic of each drug. Vd is used to characterize drug distribution since it relates the amount of drug in the body to the concentration of drug in the blood (or plasma). (Gonzalez, Coughtrie e Tukey, 2010) Knowing Vd values and absolute bioavailability, dose can also be calculated.

(2) Volume of distribution (Gonzalez, Coughtrie e Tukey, 2010)

$$Vd\ (L\ /kg) = \frac{amount\ of\ drug\ in\ the\ body}{Concentration\ in\ the\ fluid}$$

Vd is determined by the binding of the drug to tissues or plasma proteins. As plasma proteins like albumin and α_1-acid glycoprotein prevent the diffusion of the drug to extra-vascular compartments, Vd tends to be lower when comparing to a drug with no affinity for protein binding. (Gonzalez, Coughtrie e Tukey, 2010) Awareness of how much Vd is altered allows clinicians to determine the best strategy for dose adjustment. Increased Vd is observed in edema or infections and results in lower concentrations of the drug in the plasma, which may lead to sub-therapeutic doses.

3.2.2. Distribution and renal impairment

Changes in distribution may be due to fluid retention, changes in plasma proteins levels or a combination of both, consequently increasing the volume of distribution of the drug which can be justified by equation 2. (Gibaldi, 2004)

Concentration of protein-drug complexes are decreased in renal impaired patients because levels of plasma albumin and α_1-acid glycoprotein are altered due to hypoalbuminemia, accumulation of toxic substances that compete with the drug for the binding sites of the plasma proteins and conformational changes of the proteins' binding sites. Hypoalbuminemia requires the measurement of free drug for a more accurate guide for drug dosing than analysis of total drug. Since plasma proteins have low ability to bind to the drug, the same can be expected to happen in tissue binding. (Gibaldi, 2004)

Acidic drugs are the most influenced by renal impairment, either in CKD or AKI. Acidic drugs bind to albumin which may be reduced in renal impaired and is extremely reduced in NS leading to an increase in volume of distribution. Phenytoin is an example, of an acidic drug which has altered plasma protein binding in renal dysfunction states. In patients with normal renal function, 92% of the phenytoin is bounded to serum albumin, however, in severe renal impairment patients, unbound drugs increase from 8% to 16%. On the other hand, levels of α_1-acid glycoprotein are often higher in hemodialysis patients, which rarely affect protein binding of basic drugs. (Atkinson, 1999) Basic and neutral drugs bind to α_1-acid glycoprotein

and so, are not affected by renal impairment. Protein binding and volume of distribution tends to be normal.

Clinical consequences of these alterations are difficult to predict. Impaired binding increases the concentration of unbound protein which can result either in enhanced clearance or higher incidence of adverse effects. The overall effect is the reach of a new steady state where total plasma drug concentration is less when compared with healthy subjects. (Gibaldi, 2004) (Lam *et al.*, 1997)

Volume of distribution tends to increase both in CKD and AKI patients due to fluid excess, rising, consequently, the concentration of free drug. In patients with End of Stage Renal Disease, volume of distribution is rarely decreased but, if so, is due to reduced binding to tissue which happens in drugs like digoxin, pindolol or ethambutol. (Verbeeck e Musuamba, 2009) (Loo e Dowling, 2017) In AKI several phenomena can happen: alterations of the blood flow in the splanchnic circulation, muscle and fat, an uprise of the concentration of uremic toxins and hypoalbuminemia. (Gibaldi, 2004) Therefore, there is usually an increase of the unbound fraction of the drug and also in the apparent volume of distribution. (Philips *et al.*, 2014)

Albumin has a shorter half-life and a higher degradation rate and, due to sepsis and capillary leakage (which commonly happens in AKI), albumin distribution is also altered in serious ill patients. Additionally, studies demonstrate that these patients have reduced gene transcription of albumin due to low insulin activity and protein malnutrition, leading to a decrease in albumin concentrations. (Nicholson, Wolmarans e Park, 2000)

3.3. Metabolism

Metabolism is the process by which drugs suffer biochemical transformations. Sometimes, the expected effect is achieved by the administered drug while other times by its metabolites. In most cases, metabolites are inactive. Metabolism may be an extremely variable process that depends not only on chemical properties of the drug but also on the individual's biological environments. Several organs are able to metabolize compounds (liver, kidney, intestine, lung, skin, prostate, brain), being the liver the principal organ due to the abundance and diversity of metabolic enzymes (Gonzalez, Coughtrie e Tukey, 2010). Metabolic enzymes transform the drug to new chemical entities with, sometimes, different pharmacological activity. These

reactions are called biotransformation and it can result in changes in the molecular structure, decreasing or increasing (activating), their pharmacological activity (Lamattina e Golan, 2009)

As enteric venous circulation goes from GI tract directly to liver through portal vein, drugs administrated orally can suffer metabolism before their absorption to the systemic circulation, limiting the amount of drug that reaches the bloodstream, a phenomena called first pass metabolism. (Lamattina e Golan, 2009)

Drug metabolism can be divided into two phases: phase I – reduction and oxidation (redox) reactions and phase II – conjugation reactions. Drugs may undergo through each one or both phases.

Phase I redox reactions may result in increased or decreased pharmacological activity of the compound. (Lamattina e Golan, 2009)Cytochrome P450 (CYP450) is a superfamily of enzymes present in the liver that are involved in these reactions. Specific isoenzymes of the CYP450 family are involved in the majority of the phase I reactions that occur in the liver. Depending on the frequency of occurrence of CYP450 there are three types of metabolizer phenotype: poor, intermediate and ultrarapid. Levels and activity of isoenzymes differ from an individual to another and can be misrepresented in some pathologies. An understanding of the quantity and the presence of metabolic isoenzymes is crucial to a better knowledge of the efficacy of drug therapies.

Conjugation reactions involve the formation of covalent bonds between the drug or the phase I metabolite with a substrate. (Lamattina e Golan, 2009) The product of the phase II reaction has typically no pharmacological activity and is water-soluble to facilitate the elimination process.

3.3.1. Metabolism and renal impairment

Metabolic clearance of drugs is altered in renal impaired patients. The impact of renal impairment on drugs' metabolism depends on the metabolic pathway and the drug. In most cases, it is uncertain how much renal impairment can affect metabolism and at which stage of renal disease the changes in drugs' clearance are observed. (Atkinson, 1999) In renal dysfunction patients not only the activity of many metabolizing enzymes (mostly selected isoforms of CYP450 enzymes and N-acetyltransferases), is compromised but also the activity of transporters in the intestines, liver and kidneys. (Verbeeck e Musuamba, 2009) Changes in

the activity of transporters and metabolizing enzymes directly affect the bioavailability of the drug and systemic drug exposure. Levels of CYP3A4, CYP1A2, CYP2B6, CYP2A9 and CYP2D6 are diminished in renal impaired patients when compared with healthy subjects due either to direct inhibition of their active site by uremic toxins or by downregulation of the enzyme synthesis leading to an excessive exposure and bioavailability of drugs that are metabolized by these isoforms. (Ladda e Goralski, 2016) Drugs that undergo first pass metabolism usually are CYP3A substrates, an enzyme with reduced activity in renal impaired patients. Reduced first pass metabolism leads to increase bioavailability of the drug.

In CKD, the effect of renal impairment on both reduction and oxidation reactions is minimal, depending however, on the drug. For example, oxidation in phenytoin is enhanced while reduction of cortisol is diminished. (Lam *et al.*, 1997)

AKI can affect both reduction and oxidation reactions and metabolite excretion from hepatocytes due to reduced expression and translation of CYP450 and endothelial dysfunction caused by accumulation of a competitive inhibitor. Inflammation frequently occurs in patients with AKI leading to high production of IL-6 which reduces the inductibility of the CYP isoforms and leads to an increase of cortisol levels, which competitively inhibits the metabolism of CYP substrates. (Blanco *et al.*, 2019) (Philips *et al.*, 2014)

Drug transport has a remarkable impact on the PK of the drug and is also influenced by renal dysfunction because transporters are highly expressed in the intestine, the kidney and the liver. Organic Anion Transporting Polypeptides (OATP), P-glicoprotein (P-gp) and Multi-drug resistance associated protein (MRP2) are enzymes that can be affected in renal impaired patients, increasing exposure of the drug. Inhibition or stimulation of the transporters activity can lead to clinical changes in drug efficacy or toxicity. (Verbeeck e Musuamba, 2009) Alteration of OATP levels can limit hepatic elimination while alteration of levels of P-gp and MRP2 affect drug removal. Levels of the efflux and influx transporters are differently altered in different organs. (Gibaldi, 2004)

3.4. Excretion

Excretion is the process by which the drug is expulsed from the body. Biotransformation reactions facilitate the elimination of drugs and their metabolites by modifying their structure to more hydro-soluble drugs. Some drugs are secreted by the liver to the bile and need a

complete pass through the intestine to be eliminated in the faeces. These drugs may pass the enterohepatic circulation, be absorbed in the intestines, re-enter the hepatic portal-vein and be back to the liver. Drugs can also be excreted via sweat, saliva, tears, bile and breast milk. However, non-renal excretion levels are quantitatively insignificant. (Gonzalez, Coughtrie e Tukey, 2010)

The kidney is the main excretory organ. Renal excretion involves a balance of three major processes:

- Glomerular filtration;
- Tubular reabsorption;
- Tubular secretion.

Firstly, the free drug is filtered in the glomerulus. Then, in the proximal tubule, it will be passively or actively reabsorbed back into the systemic circulation. Drugs may also pass through active tubular secretion, where unbound drug in plasma is transported into the urine. This transport is mediated by organic anionic transporters (OAT), organic cationic transporters (OCT) or P-gp. (Loo e Dowling, 2017) The main mechanism of renal excretion of drugs is the tubular secretion, rather than glomerular filtration. (University of Nottingham, [s.d.])

Glomerular filtration occurs under positive hydrostatic pressure through pores localized in the glomerular membrane. Small polar drugs are filtrated from the blood to the glomeruli while plasma proteins and drug-protein complexes are not filtered. (Lamattina e Golan, 2009) The efficacy of glomerular filtration is influenced by the protein binding and by the blood flow rate. Tubular reabsorption, in the distal tubule, most of the water and specific compounds are reabsorbed back into the blood occurs, increasing the concentration inside the tubule. This allows polar molecules to remain inside the tubule whereas lipid-soluble drugs returned to the plasma until they are metabolized to more polar compounds. Tubular secretion lowers the plasma concentration of unbound drug, enabling the dissociation of the complexes and the elimination of the drug.

Changes in overall kidney function may affect one or all of the processes and, therefore, the drugs' elimination. There is a variation trough time either in healthy or injured subjects.

3.4.1. Clearance

Drugs' elimination can be described by the parameter Clearance. Clearance (Cl) is the apparent volume of blood cleared of drug in a certain period of time and it can be referred to by a particular excretory organ (kidney - Cl_k, liver - Cl_H, or other excretory routes - Cl_{other}) or the whole body (total or systemic clearance). (Gonzalez, Coughtrie e Tukey, 2010) Renal clearance of a drug is measured by its rate of excretion in urine and changes in its plasma concentration at a certain time point. (Gonzalez, Coughtrie e Tukey, 2010) Since only the unbound fraction of the drug can be eliminated, protein binding is one major factor that affects renal clearance as GFR, secretion ($Cl_{secretion}$) and reabsorption ($Cl_{reabsorption}$) that occur in the kidney.

(3) Renal Clearance (Lea-henry *et al.*, 2018)

$$Cl = CL_K + Cl_H + Cl_{other}$$

$$Cl_K = (Fu \times GFR) + Cl_{secretion} - Cl_{reabsorption}$$

3.4.2. Elimination half-life

The half-life ($t_{1/2}$) of a drug is the time that takes to the dose administrated be reduced by 50%. This parameter is dependent both from Cl and Vd as it increases while Cl decreases.

(4) Elimination half-life ($T_{1/2}$) (Lea-henry *et al.*, 2018)

$$t_{1/2} = \frac{0.693 \times Vd}{Cl}$$

Elimination half-life is a critical parameter for the determination of the duration of action and potential for side effects after a single or multiple dose and for establishing dosing frequency. (Lea-henry *et al.*, 2018) Drugs with prolonged $T_{1/2}$ need more time to reach steady-state concentrations.

$T_{1/2}$ cannot be the parameter used as index for drug elimination because drugs can "vanish" due to metabolism and formation of metabolites with either therapeutic of toxic effects.

However, $T_{1/2}$ provides a good indicator for assess time to reach steady state after introduction of a certain regimen, time that takes to remove the drug from the body and to estimate the suitable dosing interval. (Gonzalez, Coughtrie e Tukey, 2010)

3.4.3. Excretion and renal impairment

Excretion is the pharmacokinetic most affected process by renal diseases. In renal impairment, there is a decreased amount of functioning nephrons, a reduced renal blood flow, reduced GFR and reduced tubular secretion, leading to overall reduced elimination and prolonged half-life of drugs mainly excreted by the kidney. Drugs excreted by other routes behave similarly when compared with healthy patients. (Loo e Dowling, 2017) (Bettinger *et al.*, 2016)

The three excretion processes (glomerular filtration, tubular reabsorption and tubular secretion) work together to form an efficient pathway in which drugs are removed from the body. As filtration rate gradually decreases in renal impairment, some data suggest that tubular secretion remains functioning, thus providing renal clearance for some drugs up to a limit. (Gibaldi, 2004)

Each of the determinants of renal excretion are influenced by other processes that are also compromised in renal diseases. The most important is glomerular filtration because it is disturbed by protein binding, which is decreased in renal impaired patients, principally for acidic drugs. Since GFR is mostly affected by kidney diseases, $T_{1/2}$ is prolonged proportionally to an increase in Vd or a decrease in total clearance. (Lea-henry *et al.*, 2018) Although glomerular filtration and tubular secretion are also compromised at different levels, renal clearance of most drugs appears to vary in direct proportion to GFR or measured GFR.(Verbeeck e Musuamba, 2009)

Transporters also exist in the kidney therefore, as explained above, changes in transporters not only have an impact on drug metabolism but also on drug clearance. OAT and OCT localized in the proximal renal tubule are exclusive for anions or cations, respectively, but have low specificity for substrates. Active tubular secretion tends to be nonspecific between two anions or two cations, increasing therefore, the possibility for drug-drug interactions. (Lam *et al.*, 1997) Drug-drug interactions may decrease clearance due to competitive binding to active transporters and saturable process. (Lea-henry *et al.*, 2018)

According to equation 4, an increase in Vd or a decrease in Cl lead to an increase in $T_{1/2}$ in the same proportion. However, the reciprocal relationship does not work when the disease affects Vd, which is the case for both CKD and AKI. Changes in protein binding may affect Cl and Vd so, unpredictable changes to half-life may occur. (Gonzalez, Coughtrie e Tukey, 2010)

In renal impaired patients, the half-life of the metabolites should also be considered because if dose adjustment is not accurate, accumulation of toxic metabolites can occur, especially in continued drug therapy as in morphine, meperidine, allopurinol or cyclophosphamide. (Lea-henry *et al.*, 2018) (McAinsh *et al.*, 1980)

4. Dose Adjustment in Renal Impairment

Suitable dosing in renal impaired patients must maximize therapeutic effect, minimize toxic effects and have an economic impact not only on the patient but also on the healthcare system. Decreasing adverse reactions and hospitalizations, costs in health decrease for patients with renal dysfunction. Appropriate dose adjustment must avoid unnecessary expenses related to drug toxicity to the patient and to health system.

To optimize treatment regimens in patients with kidney diseases, it is essential to understand how the disease affects the drug pharmacokinetics (PK). Prescribing drugs to kidney impaired patients must take into consideration that kidney disease may be chronic or acute, that it has multiple effects on PK and that each situation has different approaches when it comes to adjusting the dosage. (Lea-henry *et al.*, 2018) Failure in assessment of the changes in pharmacokinetics can lead to lack of efficacy or adverse events.

During the development phase of a drug, posology is determined in clinical trials which are done in patients with normal or mild renal impairment. Therefore, there is limited and unspecific data and trials about changes that occur in pharmacokinetics in renal impaired patients. This may lead the Sponsor to contraindicate the drug in patients with renal impairment by safety concerns. Both supra and sub-therapeutic concentrations can occur when dose is not modified. Sub-therapeutic dosage increases the risk for treatment failure whereas supra-therapeutic dosage can predispose the patient to accumulation of toxic metabolites.

Pharmacokinetic is a mathematical driven science. Therefore, changes in PK parameters can be quantified to allow a more precise adjustment in dosing regimens. Adjustment of drug dosage should be considered when drugs are mainly excreted by kidney both unchanged and as an active metabolite or when the drug has narrow therapeutic window. Although the minimum change in kidney function to demand dose adjustment is not defined, it is usually not needed if it is less than 30%. (Lea-henry *et al.*, 2018) However, dosage adjustment must be adequate not only to the level of kidney dysfunction, but it should also consider the risk of drug accumulation, the characteristics of the drug, the time treatment and the initial dose. Due to lack of specific information and individual and disease variability, the strategies to dosage adjustment must be analyzed in a case-by-case basis. (Roberts *et al.*, 2018)

Concentration-time profile of the drug is determined through several PK parameters. Measuring changes in PK that occur in renal impairment allows the modification of the dosing regimen in order to optimize the drug concentration required to therapeutic effect. As clarified above, Cl and Vd are the major PK parameters affected by kidney injury in both chronic and acute conditions. To establish adjustment of dosage in individual therapeutics, four major parameters must be considered related to drug disposition: bioavailability, volume of distribution, clearance and half-life.

Moreover, before choosing a drug, knowledge of its therapeutic index is also essential to understand the margin of safety between the dose needed to minimal effect and the minimal dose that produces adverse effects.

The dosage regimen is defined by the loading dose, the maintenance dose and the dosing interval. (Verbeeck e Musuamba, 2009) Dose adjustment assumes that only renal clearance is affected, while other PK parameters remain unchanged. Nevertheless, more than one parameter is frequently affected by renal impairment which means that approaches may not be accurate. Strategies must be chosen according to the disease stage, the drug to administrate and the patients' characteristics.

Kidney diseases are very heterogeneous, varying in severity and clinical effects on the kidney structures – blood vessels, glomeruli and nephrons. Each condition – acute or chronic, is affected in different ways, has different treatments and, therefore, different preferential strategies for dose adjustment. Approaches in Chronic Kidney Disease (CKD) patients must be different from those used in Acute Kidney Injury (AKI) patients because drug clearance and the distribution of the drug differ in short time frames. (Roberts *et al.*, 2018)

There are several strategies that can be used when adjusting dosage regimens. More than one strategy can be adopted:

- administration of a loading dose;
- determination of the maintenance dose;
- closer therapeutic drug monitoring.

Nonetheless, designing optimal dosages for renal impaired patients is still a challenge and depends on the availability of an accurate characterization of the PK parameters and kidney function. (Gilbert, 2013)

4.1. Measuring Kidney Function

The best index of kidney function is Glomerular Filtration Rate (GFR), both in healthy people and in patients. Its decline helps to measure disease progression. It is affected by intra-individual factors like age, gender, body size, concomitant drugs or diseases or pregnancy, however, the normal level of GFR is 130 ml/1.73 m^3 for men and 120 ml/1.73 m^3 for women. (Richard, J Johnson; John e Floege, 2014) Since GFR cannot be assessed directly, clearance measurements of endogenous or exogenous solutes mainly excreted by glomerular filtration are used to measure or estimate GFR. (Gilbert, 2013) Inulin is the golden standard as an exogenous filtration marker while creatinine is the major standard as an endogenous filtration marker. The latter does not need to be administrated and is the most popular choice because it is less expensive and there is more experience with it. (Stevens *et al.*, 2006) Determination of creatinine clearance requires a 24-hour urine collection which can be difficult to obtain due to patient compliance. Typically, equations use serum levels of creatinine. However, serum creatinine alone is not recommended to classify CKD since it can lead to misclassification of the severity. (Gilbert, 2013) Equations have been developed to estimate GFR, taking into account other factors that affect GFR.

(5) Cockcroft-Gault Formula (DW e MH, 1976)

$$\frac{(140 - age) \times weight}{72 \times creatinine} \times 0.85\ (if\ female)$$

The Cockcroft-Gault Formula is the most used yet the oldest and, according to some, the less accurate equation to estimate creatinine. (Rostoker *et al.*, 2009) (Gilbert, 2013) It depends on intra-individual factors like gender, age, body weight and serum creatinine values which can over or underestimate GFR whether the patient is obese or older.

(6) Four variable Modification of Diet in Renal Disease Formula (Andrew S. Levey *et al.*, 2012)

$$175 \times creatinine^{-1,154} \times age^{-0,203} \times 0{,}762\ (if\ female) \times 1.210\ (if\ black)$$

The Modification of Diet in Renal Disease (MDRD) Equation is a set of equations derived from the database of epidemiologic study with the same name and it claims to be more accurate than the Cockcroft-Gault Formula because it used a standardized method for creatinine measurement. There are two equations related, with six or four variables. (Gilbert, 2013) The equation has not been validated in patients older than 70, but an MDRD-derived eGFR may still be a useful tool for providers caring for patients older than 70. (Levey *et al.*, 2018)

(7) Chronic Kidney Disease Epidemiology Collaboration Formula (Levey *et al.*, 2018)

If female:

Creatinine < 0.7 mg/dL: $144 \times (\frac{creatinine}{0,7})^{0,329} \times 0,993^{age} \times 1.159\ (if\ black)$

Creatinine > 0.7 mg/dL: $144 \times (\frac{creatinine}{0,7})^{1,209} \times 0,993^{age} \times 1.159\ (if\ black)$

If male:

Creatinine < 0.9 mg/dL: $141 \times (\frac{creatinine}{0,9})^{0,411} \times 0,993^{age} \times 1.159\ (if\ black)$

Creatinine > 0.7 mg/dL: $141 \times (\frac{creatinine}{0,9})^{1,209} \times 0,993^{age} \times 1.159\ (if\ black)$

The CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) Creatinine equation is the most recent set of formulas created to estimate GFR. It is based on the same four variables than the MDRD equation but on one hand it can model the relationship between estimated GFR and serum creatinine and, at the same time, has an independent relationship between age, gender, race, body mass index diabetes and organ transplantation. (Richard, J Johnson; John e Floege, 2014) It claims to be more accurate than the MDRD equation because it was developed from a large database of subjects with different characteristics including subjects with and without kidney disease, being the recommended method for estimating GFR in adults. (Gilbert, 2013) The controversy about which is the best formula is not closed yet.

Estimated GFR is essential for clinical practice although, all equations previously mentioned are not validated for children of elderly. (Pottel *et al.*, 2016) Nevertheless, GFR equations are not directly used to classify a patient into a disease stage because they are only useful in stable patients and must be analyzed in context with the patient's stage of disease.

For CKD, estimation of GFR is essential for the detection, evaluation and management of patients with kidney disease. It allows clinicians to determine the stage of CKD and, consequently, estimate the prognosis. In AKI, levels of serum creatinine are not constant over time so, patients are staged according to the rate of rise of the marker in the blood. (Richard, J Johnson; John e Floege, 2014)

4.2. Loading Dose

Loading dose (D_L) is a higher initial dose given to a subject to quickly achieve the target concentration. Since D_L aims to rapidly reach the minimal dose with therapeutic effect, changes in clearance will not affect the dose given. Therefore, when other PK parameters than Clearance are not affected in renal impaired patients, the loading dose does not need to be changed. (Roberts *et al.*, 2018) If a loading dose is not administrated, it will take longer to reach the steady-state concentration. If a physical examination shows normal values of fluid volume, usually, the same loading dose is administrated both in renal impaired patients and healthy subjects. (McIntyre, Shaw e Eldehni, 2012) However, increasing the loading dose may be a method used in cases where Vd is increased, like in Nephrotic Syndrome, or when a delayed onset of action is not beneficial to the patient. (Gilbert, 2013) D_L is calculated by equation 8, where target C is the desire plasma concentration and F is bioavailability.

(8) Loading Dose (D_L) (Roberts *et al.*, 2018)

$$D_L\ (mg/ml) = \frac{target\ C\ \times Vd}{F}$$

Vd is often increased in renal impairment which can be challenging to the dose adjustment of drugs with narrow therapeutic index. Loading dose increases in proportion to Vd. Since half-life is prolonged in renal impaired patients, as discussed above, a reduction in the dose administrated delays achievement of therapeutic concentrations. (Richard, J Johnson; John e Floege, 2014)

Administration of a loading dose is common when a drug has a longer half-life and rapid onset of action is needed to achieve target plasma concentrations.

4.3. Maintenance Dose

In renal impaired patients, drugs are frequently administrated in repeated doses or as continuous infusion to preserve a steady-state target concentration within the therapeutic window. (Gonzalez, Coughtrie e Tukey, 2010) For that, the rate of elimination and the rate of administration must be the same. Maintenance dose (MD) rate is thus determined by Clearance and depends on the measured or estimated values of GFR.

(9) MD for multiple doses (Roberts *et al.*, 2018)

$$MD\ (mg/h) = Cl\ \times target\ C$$

(10) MD for continuous infusion (Roberts *et al.*, 2018)

$$MD(mg/dose) = MD\ (mg/h) \times dosing\ interval$$

If nonrenal Clearance is unchanged, MD should be reduced in proportion to renal elimination and progression of the disease and this is evaluated by fraction of active drug excreted unchanged (*fe*). (Richard, J Johnson; John e Floege, 2014) The fraction excreted unchanged (*fe*) is the portion of active drug eliminated by kidney that allows to quantitative measure the contribution of renal excretion to total drug elimination. Values of *fe* close to 1 (one) means that the drug is only excreted by the kidneys while values close to 0 (zero) indicates that the drug is mostly metabolized. Knowledge of *fe* provides guidance for adequate dosage modification for patients with different stages of renal impairment. Since dose should be adjusted in proportion to the renal function of the patient, an increase in the fraction of drug eliminated unchanged in urine increases the need for dose modification. (Tozer e Rowland, 2006) (Doogue e Polasek, 2011)

(11) Fraction Excreted unchanged (*fe*) (Tozer e Rowland, 2006)

$$fe = \frac{Cl_K}{Cl_{total}}$$

There are three methods to adjust MD, reduction of the dose, increasing the dosage interval or a combination of both.

4.3.1. Reduction of the MD

One strategy to reach therapeutic effect of a drug in renal impaired patients is to reduce the maintenance dose given at each time point without changing the dosing interval. This strategy aims to administrate a reduced amount of drug at a given dosage interval to renal impaired patients. There is, however, a risk for underdosing, when the drug to be administrated has a short half-life and requires high concentrations to have therapeutic efficacy. (Fabre e Balant, 1976)

This approach should be used in drugs with low therapeutic index and when the peak concentration is not critical to therapeutic effect. (Gilbert, 2013) (Richard, J Johnson; John e Floege, 2014)

Figure 4 - Reduction of Maintenance Dose (adapted from Richard, J Johnson; John e Floege, 2014)

4.3.2. Increasing dosing interval

On the other hand, dosing frequency changes depend on the toxicity of the drug. If dosing interval is increased, maximum concentration (Cmax) will be nearly the same as in health patients. Increasing the dosing interval is not always appropriate because a long dosing interval requires a high Cmax to achieve an adequate drug concentration and a strictly patient compliance. (Fabre e Balant, 1976)

This strategy is suitable for drugs that require a peak concentration to be effective and for drugs with prolonged half-life. (Lea-henry *et al.*, 2018)

Figure 5 - Increasing dosing interval (adapted from Richard, J Johnson; John e Floege, 2014)

4.3.3. Dose reduction and increased dosing interval

For some drugs that are extensively excreted by the kidneys and with narrow therapeutic index, strict control is needed.

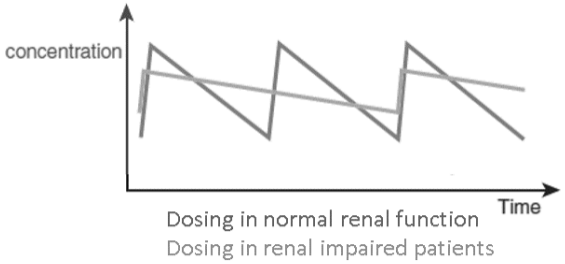

Figure 6 - Combination method (adapted from Richard, J Johnson; John e Floege, 2014)

4.4. Therapeutic Drug Monitoring

Therapeutic Drug Monitoring (TDM) is a clinical activity that measures concentrations of a drug in blood or plasma at regular time periods. (Junaid *et al.*, 2019) It aims to prevent the occurrence of adverse effects or treatment failure and specially to provide information for guidance on dosing and dose adjustment for clinicians. (Richard, J Johnson; John e Floege, 2014) It is essential to guarantee that drug concentration is inside of the therapeutic index for each patient. (Junaid *et al.*, 2019) There are several approaches to measure drug concentrations in blood, but they are not in the scope of this work.

TDM is necessary for individualization of drug dosage and therapy. Intra and inter-individual factors significantly affect drug therapy leading to different responses to the same dose

administrated in different patients. Therefore, adequate monitoring is needed to ensure that maximal effectiveness is achieved.

Beside monitoring patient compliance, therapeutic drug monitoring also helps monitoring and detecting drug-drug interactions, which frequently happens in patients with kidney dysfunction. (Junaid *et al.*, 2019)

4.5. Principles for Dosage Adjustment

In 1913, Paul Ehrlich stated the principle "go fast, start high" to be used when adjustment the dosage for antibiotics, antivirals and later, for cytostatics for intensive care unit. (Ehrlich, 2003) This principle endorses that the best approach is to start with high doses to rapidly achieve target concentrations. Later, in 1995, Jerry Gurwitz establish a second principle "start low, go slow" to be applied in drugs with therapeutic effect in the Central Nervous System. This second principle recommends reducing the initial dose and increasing it with close monitoring. Both *mottos* can be currently applied to define the adequate dosage for each patient.

Before prescribing any drug to a patient with CKD or AKI, some endorsements can be advantageous:

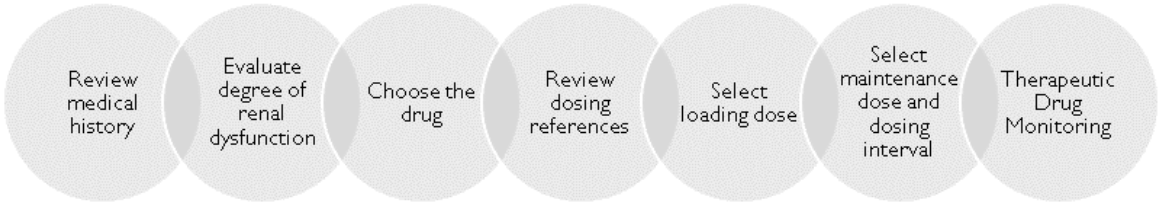

Figure 7 - Recommendations when prescribing for patients with renal impairment (adapted from Hassan et al., 2009)

An initial assessment is necessary to consider previous prescribed drugs, current medications and to collect known history of drug allergies or sensitivity in order to avoid drug-drug interactions. In patients with renal dysfunction, medication should be regularly re-evaluated to ensure that doses are still appropriate according to the disease stage and have therapeutic effect. Concomitant diseases are relevant information since it allows the anticipation of changes in volume of distribution or plasma protein levels. Evaluation of the stage of renal

impairment through Glomerular Filtration Rate is the most trustworthy method of kidney function and the basis for dosage adjustment. There are several equations to estimate creatinine clearance, previously detailed. Clinicians must be attention to nephrotoxic drugs because they should not be prescribed in patients with kidney disorders to avoid more complications in the functional nephrons. Most used nephrotoxic drugs are listed below in Table 6 and drugs with discouraged used in renal impairment in renal impairment are described in Table 7.

Table 6 - Potentially Nephrotoxic Drugs (adapted from Richard, J Johnson; John e Floege, 2014)

Potentially Nephrotoxic Drugs	
ACE inhibitors	**Antifungals**
Aminoglycosides	Amphotericin
Amikacin	**Calcineurin inhibitors**
Gentamicin	Cyclosporin
Tobramycin	Tacrolimus
Antivirals	**Chemotherapeutics**
Acyclovir	Cisplatin
Cidofovir	Ifosfamide
Foscarnet	**Lithium**
Indinavir	**NSAIDs**
Famaciclovir	**Sulfonamides**
Valaciclovir	**Proton pump inhibitors**
Ganciclovir	**Radiocontrast media**

Table 7 - Drugs with discouraged used in renal impairment (adapted from Richard, J Johnson; John e Floege, 2014)

Drug	Justification
Morphine	Accumulation of active metabolites
NSAIDs	Probable nephrotoxicity
Aminoglycosides	Nephrotoxicity
Vancomycin	Nephrotoxicity and ototoxicity
Tetracyclines	Probable nephrotoxicity, azotemia
Anticoagulants (including warfarin)	Bleeding and calcification
Spironolactone	Hyperkalemia
Metformin	Lactic acidosis

Several drugs already have prescription information for different stages of kidney disease. The most important sources of information are listed in Table 8. Nevertheless, it is wise advice that clinicians should start the revision by examining the most recent published references. (Jogia e Brien, 2009)

Table 8 - Common reference sources (adapted from Jogia e O'Brien, 2009)

Reference Source	Characteristics
British National Formulary	Simple to use, mentions manufacturers' advice. Limited specialist advice, not frequently updated (every six-months)
Summary of product characteristics	Detailed information (with dosing for different stages of renal impairment), easy access, frequently updated Limited access (only with license), some do not have information for renal impairment
Drugdex	Detailed information US-based information
The Renal Drug Handbook	Information regarding administration, drug interactions and common clinical practice Not frequently updated, difficult access

Risks and benefits of each drug must be evaluated and measured before and after prescription. Deprescribing can be defined as "the systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goals". (Scott *et al.*, 2015) If deprescription is needed to reduce possibility of adverse effects, then it must be considered. (Whittaker *et al.*, 2018) Prescribing drugs for patients with kidney diseases can be challenging nevertheless, it provides important data and offers a great opportunity to improve therapy in a high-risk population.

4.5.1. Dosing in Chronic Kidney Disease

In CKD patients, decline in GFR is progressive and can be stable for weeks or months. Each stage of CKD may require a different dosing adjustment. An approach to modify dosage in CKD patients is to assume that clearance decreases in the same proportion as GFR while non-renal clearance remains unchanged. (Roberts *et al.*, 2018) However, this approach is limited because changes in non-renal clearance also occur and it is very challenging to quantify them.

An initial loading dose can be administrated when a rapid onset of action is needed to overcome changes in the bioavailability of the drug. Maintenance dose and dosing frequency should be accessed in a case by case basis. Drug reduction may also be necessary for drugs that undergo non-kidney clearance.

4.5.2. Dosing in Dialysis patients

Dose adjustment in patients in dialysis is a challenge because clearance of the drug depends on several variables at the same time: molecular weight of the drug, protein binding, volume of distribution and technical aspects of the procedure, including size and permeability of the dialyser, as well as blood and dialysis flow rate. (Smyth, Jones e Saunders, 2016)

Dialysis is used to remove toxic substances from the body, drugs and active metabolites included. (Verbeeck e Musuamba, 2009) Administration should be avoided immediately before dialysis to maximize therapeutic effect and minimize excessive removal of drug and therefore sub-therapeutic effect.

It is beneficial to administrate drugs in dialysis days to enhance compliance and to guarantee that dose given at the end of dialysis is adequate to achieve the desirable concentration for therapeutic effect. Drugs that are not significantly cleared by dialysis are administrated at time points independent of dialysis days while drugs that are significantly cleared in dialysis require administration of a supplemental dose after the procedure to compensate dialysis removal. (Hon, 2017) Such is the case of some analgesics like morphine and aspirin, antibiotics like amoxicillin, vancomycin or ciprofloxacin, and metformin. Vancomycin is often used to treat Gram-positive infections in hemodialysis patients. The removal by low-flux dialysis is low. Therefore, the classical prescription of vancomycin was at the end of treatment, once a week or every two sessions. However, with high-flux dialysers, vancomycin clearance in dialysis is increased, resulting in lack of therapeutic response. Therefore, vancomycin is currently infused during the last hour of the dialysis session. (Taylor e Allon, 2010) With this regimen, vancomycin therapeutic concentrations are achieved.

An important factor that influences drug removal is its rate of protein binding. Some drugs that highly bound to plasma proteins are not removed by dialysis. Some examples are of phenytoin, valproic acid, and rivaroxaban. A closer monitoring is needed, as there is risk of

accumulation. (Kerns e Di, 2009) This is particularly important when treating drug intoxications, as they need hemoperfusion for its elimination from the body. (Shannon, 1997)

Another approach to dose modification in dialysis patients is to calculate the amount of drug eliminated during dialysis and replace it after the dialysis session. The fraction of the drug that was eliminated can be calculated knowing the total fraction eliminated by dialysis (f_D), the overall elimination rate constant (k_D) and the duration of the dialysis (t).

(12) Fraction of the drug that was eliminated in dialysis (Verbeeck e Musuamba, 2009)

$$Fraction\ of\ eliminated\ drug = f_D \times [1 - e^{k_D - t}]$$

Administered dose can also be estimated by knowing the maximum concentration (C_{max}) and serum concentration of the drug after dialysis ($C_{post\ HD}$)

(13) Dose to administrate after dialysis (Loo e Dowling, 2017)

$$D_{post\ HD} = V \times (C_{máx} - C_{post\ HD})$$

When prescribing for dialysis patients, it is important to realize that they are more susceptible to drug toxicity. By this time, some guidance can be used as reference sources for dose adjustment for a chronic dialysis patient. 'Start low and go slow' is the best approach: look closely for adverse effects and increase the dose after evaluation following an appropriate time interval if no toxicity is observed.

4.5.3. Dosing in Acute Kidney Injury

In AKI, there is a high inter-patient variability due to the different causes of disease. This fact enhances the difficulty of delivering a standard method. AKI is a common consequence of some conditions and mostly occurs in hospitalized patients. Moreover, dosage adjustment is more difficult because patients are being treated for major comorbidities and by specialists other than nephrologists. Furthermore, besides AKI, the underlying condition also changes the

pharmacokinetics of the drug, volume levels and organ physiology hence, drug concentrations can be very heterogeneous. (Roberts *et al.*, 2018)

In AKI there are significant changes in pharmacokinetics, which calls for a close drug monitoring and dosage adjustment. (Blanco *et al.*, 2019) Furthermore, before prescribing any drug to a patient with AKI, it is essential to review the entire chart to ensure that there will not be harmful interactions.

A loading dose can be beneficial for drugs that need a rapid onset of action and an intravenous administration can evade potential changes in oral absorption, as happens in CKD. However, since in AKI renal function is declining in short time periods, dose adjustments are needed more frequently when compared with CKD patients.

As AKI patients are often submitted to hemofiltration, hemodiafiltration, plasmapheresis, plasmafiltration and hemoperfusion, considerations about drug removal by high-efficiency extracorporeal dialysis techniques also apply, falling out of the scope of this work. (Ibrahim *et al.*, 2007) (Bugge, 2001)

4.6. Special Considerations for some drugs

4.6.1. Anti-inflammatory drugs

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) should be avoided in patients with kidney dysfunction and for chronic use because of their interference with vascular mechanisms of defense against vasoconstricting insults to the kidney and their increased risk of bleeding, cardiovascular events and renal complications. NSAIDs should only be used in acute situations and at a minimal period possible. (Davison, 2019) Prolonged use of NSAIDs in renal impaired patients can be associated to AKI (indomethacin), nephritis (ibuprofen and naproxen) and fluid accumulation, worsening hypertension.

Acetaminophen (paracetamol) is a safe choice for pain relief in patients with kidney dysfunction. It does not require dose modification and is not nephrotoxic. (Richard, J Johnson; John e Floege, 2014) Acetaminophen is poorly excreted by kidneys thus, there are no clinically concerns regarding their administration to renal impaired patients. (Davison, 2019) It is an alternative to NSAIDs.

4.6.2. Analgesics

Most analgesics and their metabolites are eliminated by kidney. Thus, in renal impairment, the possibility for toxic accumulation and adverse effects like delirium, nausea, vomiting, sedation and respiratory depression is significantly increased. Analgesics are often nephrotoxic themselves. Dose adjustment in renal impaired patients is required however, dose administrated may not be enough for pain relief because the drug cannot be administrated in safe doses. (Richard, J Johnson; John e Floege, 2014)

Opioids depend on renal elimination and usually have active metabolites that can accumulate leading to adverse effects. Since decreased renal function significantly affects opioids metabolites elimination from the body, special consideration when prescribing for renal impaired patients is essential. Doses should be adequate and titrated carefully to reach effective dose with minimal adverse effects. (Richard, J Johnson; John e Floege, 2014) Opioid toxicity predispose the patient to poor analgesic effect and drug interactions. (Davison, 2019)

Tramadol, after hepatic metabolism, is converted to two different metabolites. Only one variant is active and more potent than tramadol. Which means that, accumulation of that metabolite (the O- variant) caused by insufficient renal elimination, can lead to, in rare cases, seizures and respiratory complications and drug interactions. Morphine and meperidine strongly depend on renal elimination to excrete their metabolites. Morphine metabolite accumulation increases the risk for excess sedation while meperidine metabolite accumulation lead to Central Nervous System (CNS) neurotoxicity, seizures and delirium. (Davison, 2019)

Other analgesics like oxycodone, fentanyl and methadone can be safely used with adequate dosage modification because they do not have active metabolites. (Richard, J Johnson; John e Floege, 2014) (Leo, 2014)

4.6.3. Antibiotics

Antibiotics are excreted by kidney. Thus, dose modification is often required in patients with kidney dysfunction. Nevertheless, drugs with wide therapeutic index usually do not need dose adjustment. When prescribing antibiotics for vulnerable organisms or when drug distribution is decreased at site of action, one approach is to initiate with effective doses rather that reduced doses to avoid fail of drug response. (Richard, J Johnson; John e Floege, 2014)

Aminoglycosides are excreted by the kidneys and can cause nephrotoxicity by direct tubular toxicity and irreversible ototoxicity thus, dose adjustment is essential to prevent adverse events and toxicity. A loading dose is needed to achieve peak concentration levels necessary to drug response. Dose is usually reduced while dosing interval is preserved. (Bennett, 1979) Drug monitoring is required to ensure drug response at safe drug concentrations. Glycopeptides, similar to aminoglycosides, have potential for nephrotoxicity and ototoxicity. Therefore, dose modification is required. Furthermore, toxicity is dose-cumulative between infectious episodes: therapy duration should be reduced at the minimum with regular serum monitoring of drug concentrations. (Leclrecq e Tulkens, 1999) (Richard, J Johnson; John e Floege, 2014)

Penicillins are safe to prescribe to renal impaired patients because they have wide therapeutic index, short half-life and toxicity is easily detected. Nonetheless, accumulation of penicillins may lead to neurotoxicity expressed as seizures and change in mental status which can be avoided with dose reduction. (Richard, J Johnson; John e Floege, 2014) (Bennett, 1979)

Tetracyclines elimination is significantly reduced in renal impairment. They can exacerbate uremia and renal dysfunction in patients with pre-existing renal diseases therefore, prescription is not recommended. (Richard, J Johnson; John e Floege, 2014) (Bennett, 1979)

4.6.4. Antivirals

In renal impaired patients, antivirals usually demonstrate prolonged half-life and reduced clearance. Normal doses will accumulate and may lead to reversible CNS complications expressed as dizziness, confusion, hallucinations and convulsions as well as, more rarely, seizures. Adverse effects are proportional to the administrated dose and can be stopped by discontinuing the drug. Cidofovir and foscarnet have nephrotoxicity. Acyclovir, famciclovir and ganciclovir are extensively excreted by the kidneys. Their accumulation can cause obstructive nephropathy, CNS toxicity and bone marrow toxicity (ganciclovir). Dose modification is critical to ensure drug response without any toxicity observed. However, acyclovir accumulates in dialysis patients, exacerbating toxicity.

4.6.5. Antihypertensive drugs

Clinicians must be very cautious when prescribing antihypertensive drugs in patients with abnormal renal function because there is an increased risk of renal hypoperfusion. Administration of ACE inhibitors and spironolactone to renal impaired patients increases the risk for hyperkalemia thus increasing the risk for cardiac complications as arrhythmias or altered cardiac eletroconduction. (Whittaker *et al.*, 2018) (Hartmann, Czock e Keller, 2010) ACE inhibitors are excreted by the kidneys nevertheless they can be used in renal impaired patients if administrated at reasonable doses, titrated to drug response and suspended in acute episodes of dehydration, infections or sepsis.

4.6.6. Antiarrhythmics

Most used antiarrhythmics are eliminated by the kidneys requiring, therefore, dose modification in renal impaired patients. Digoxin poisoning is a very common reason for prolonged hospital admissions in renal impaired patients. (Lea-henry *et al.*, 2018) Digoxin is a critical case because it significantly goes through renal excretion and has a narrow therapeutic index. Both maintenance dose, loading dose and dosing frequency should be adjusted due to protein binding, decreased volume of distribution and increased half-life to avoid drug accumulation. (Richard, J Johnson; John e Floege, 2014) Procainamide also needs increasing of the dosing interval because its metabolite has a longer half-life than the parent drug and can accumulate in the body. (Bennett, 1979)

4.6.7. Anticoagulants

Administrate anticoagulants to renal impaired patients, increases the risk of bleeding. Most of the anticoagulants prescribed have an increased risk for accumulation in patients with kidney diseases. Dose should be reduced or, if possible, drug should be avoided. (Richard, J Johnson; John e Floege, 2014)

Enoxaparin, a low molecular weight heparin, should be avoided in patients with renal dysfunction. The drug, even with dose adjustment, can lead to hemorrhagic disorders which aggravates with subsequent administrations. (Faull e Lee, 2007) However it may be transiently used in replacement for chronic anticoagulation before invasive procedures.

4.6.8. Antihyperglycemic drugs

Uncontrolled type 2 diabetes commonly lead to nephropathy. Metformin is the first line treatment for type 2 diabetes however, in rare cases, metformin increases the risk for lactic acidosis and AKI. (Hartmann, Czock e Keller, 2010) Nausea can also occur with prolonged administration of metformin. Adverse effects are dose related and reversible with dose reduction. Patients with diabetes and renal dysfunction need lower doses of insulin because clearance of insulin is mainly renal. If monitoring is not performed, episodes of hypoglycemia may occur. (Faull e Lee, 2007) According to FDA, metformin is discouraged with a GFR below 45 mL/min and contraindicated with a GFR below 30 mL/min. (U.S. Food and Drug Administration, 2017)

4.7. Concluding remarks

To improve prescription in renal impaired patients, cooperation between all healthcare providers is essential. Clinical pharmacist can assist clinicians with state-of-art information, which is essential to a better quality of medicines use. Joining forces is the most effective tactic to maximize drug therapy in renal impaired patients. (Hassan *et al.*, 2009)

There is lack of evidence of the changes that occur in drugs pharmacokinetics in patients with chronic or acute kidney disease. Consequently, dosage adjustment guidelines for AKI or CKD are not accurate and do not embrace enough drugs. There is an urgent need to fill the gaps to better personalize medicine and drug prescription. For both CKD and AKI, PK studies in patients in all stages are needed for renally excreted drugs to develop more reliable drug dosing adjustments. Measured GFR is the standard measure of renal function for a more accurate data integration. Finally, drug labelling should have more information about the efficacy and safety of the drug in renal impairment. (*Drug dosing consideration in patients with acute and chronic kidney disease - a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO)*, 2011)

5. Regulatory Environment for Development of New Drugs in Renal Impairment

5.1. Introduction

Patients with renal impairment are usually left out from late phase and pivotal studies of new medicinal products, by restriction inclusion and exclusion criteria. The aim of this practice is to achieve the most standardization possible of study samples. As a consequence, patients with renal impairment are often misrepresented. Data obtained in those trials are normally used for extrapolations from the general population to other sub-populations not represented in the pivotal study. Therefore, data are often incomplete, because differences can be significant.

There is an unmet need for pharmacokinetic (PK) studies during drug development in patients with mild to severe kidney disease compared to normal renal function. EMA outlines that a PK study must be performed to determine drug exposure in patients with decreased renal function.

Both European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have developed comprehensive guidelines on the evaluation of the pharmacokinetics in patients with decreased renal function. Both guidelines describe how to conduct PK studies in patients with renal impairment, addressing study design, population, sample collection, assessment of renal function, and when to conduct these studies.

The aim of this chapter is to analyze and compare recommendations detailed in the *Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function* by EMA published in 2015 and the *Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling* by the FDA released in 2010.

5.2. When to conduct PK studies in patients with decreased renal function

According to EMA, PK studies should be conducted when the renal impairment induces a risk for increased drug or metabolite exposure, for example, when renal excretion of the drug and/or the metabolite is significant. EMA also recommend PK studies for drugs eliminated by

the liver because the risk for increased exposure due to limited renal excretion must be considered. There must be special considerations if the drug is going to be given to patients on dialysis. EMA defends that PK studies are not needed for drugs for single-dose administration which prolonged elimination is not a safety problem; for drugs primarily excreted by non-renal routes and non-hepatic routes; for proteins that don't pass through glomerular filtration; for drugs without relevant systemic absorption; for drugs with hepatic elimination and for which there is available safety data indicating that there is no need for adjustments or handling of the drugs can be made in clinical practice, and for drugs not intended be used in patients with renal impairment.

According to FDA, PK studies must be conducted when the drug will be used in these patients, when the PK of the drug/metabolite is expected to be influenced (essentially for drugs excreted primarily by the kidneys) and when dose adjustment will be required. PK studies are also indicated for drugs with narrow therapeutic index and drugs with high plasma proteins binding combined with hepatic clearance. FDA consider that PK studies are not needed for drugs that are not expected to affect PK parameters like, drugs or metabolites without narrow therapeutic index and that are eliminated by non-renal routes, volatile compounds and drugs for single-dose administration.

Both regulatory agencies agree when to and when a PK study is not necessary although, EMA is more restricted.

5.3. Study design

PK studies in patients with decreased renal function aim to determine whether the extent of alterations in PK parameters requires, or not, dose adjustment. These PK studies should be conducted in otherwise healthy subjects. In some cases, depending on the safety concerns of the drug, patients with the condition in which the drug is intended to be used should be enrolled.

It is also recommended, that a healthy population should be used in the study as test group or in a 'control group' defined by EMA as "the group best representing renal function in the study population" and, not necessarily a group with normal renal function. Both agencies agree that the number of subjects enrolled in the study should be sufficient and should represent the renal function groups.

The thresholds for EMA and FDA renal function groups have slightly different values, as shown in Table 9.

Table 9 - Renal function groups (by EMA and FDA)

Group	Description	EMA: GFR (ml/min)	FDA: Estimated Creatinine Clearance (ml/min)
1	Normal renal function	>80	>90
2	Mild renal impairment	50 - 80	60 - <90
3	Moderate renal impairment	30 - 50	30 - <60
4	Severe renal impairment	<30	<30 not requiring dialysis
5	End of Stage Renal Disease (ESRD)	Requiring dialysis	<15 requiring dialysis

Both agencies acknowledge three protocol designs for trials in renal impairment – full range, reduced or staged studies. The decision to select a design over the other is due to the degree of renal clearance, impact in PK parameters and the safety profile of the drug. (Paglialunga *et al.*, 2017)

5.3.1. Protocol Designs

5.3.1.1. Full range design

The full range design includes 5 groups: three with patients with mild, moderate and severe renal impairment, one with patients on dialysis and finally a control group with healthy subjects with matching relevant characteristics.

If renal impairment is suspected to result in clinically relevant increases in drug exposure and a need for dose adjustment in patients with different degrees of impairment is anticipated, a full range design is recommended, according both to EMA and FDA. A full-range study aims to describe the relationship between renal function and drug clearance.

Both agencies agree that a full-range study should, if viable, include patients representing all groups and that the groups should be comparable to each other in respect to age, gender and weight. EMA suggests the inclusion of 6 to 8 subjects while FDA does not propose an exact number of patients. However, both agree that the sample size must be sufficient to detect meaningful differences when compared to the control group.

5.3.1.2. Reduced study design

On the reduced study design, the worst-case scenario is tested. If the results of this study confirm that severely decreased function does not change the pharmacokinetics of the drug, then it is assumed that milder grades of renal impairment will not change it either and no further study is needed. It is indicated when there are reasons to believe that a dose adjustment won't be necessary.

Both agencies outline that the study should include two groups, a test and a control group. In the test group subjects will present GFR as low as possible, not requiring dialysis, whereas the control group covers subjects with normal renal function. If changes in PK parameters are observed, more data is needed. If changes are not observed, no more studies are required.

5.3.1.3. Staged study design

FDA describes the stage study design as a Stage 2 version of the reduced study (stage 1) while EMA defines it as an extension of the reduced study.

Regardless this difference, other groups are added incrementally, ranging from the most severe to the milder, using the same principle as the reduced stage design: if a worse grade of renal impairment does not show differences to the control, a milder one will not show either.

If changes in PK parameters are observed, more data about intermediate renal function groups are needed. The decision on which renal groups should be included relies on the therapeutic indication of the drug and which groups are expected to affect the pharmacokinetics of the drug.

5.4. Drug administration

As changes in PK can be unpredictable, it is recommended to administrate the lowest effective dose for renal impairment studies. Since the drug to be studied is not intended to the treatment for renal impairment, other factors should be considered. Both agencies describe two approaches for drug administration, single and multiple dose.

5.4.1. Single-dose study

According to EMA and FDA, single-dose studies are recommended for drugs who exhibit time-independent pharmacokinetics and for those whose steady state PK can be predicted from single-dose data. In these studies, the same dose can be administrated to all renal function groups because maximum concentration is not significantly affected by decreased renal function. Usually, reduced and full design studies have single-dose administration.

5.4.2. Multiple-dose study

Multiple-dose studies, however, are indicated by both agencies for drugs who exhibit time-dependent pharmacokinetics or if steady state pharmacokinetics cannot be predicted through single-dose data. Doses to be administrated in a multiple-dose study are chosen in order to achieve drug concentrations within the clinical therapeutic window. To prevent dangerous levels of the drug or their metabolites, EMA suggests lowering the dose or to administrate the drug less frequently.

Both agencies recognize the need for a loading dose to easily achieve steady state particularly if the half-life of the drug is significantly prolonged in renal impairment.

5.5. Sample collection and analysis

According to both agencies, plasma or whole blood should preferably be collected over urine. Samples should be analyzed not only for the drug and their metabolites with suspected activity (therapeutic or adverse) but also for toxic metabolites mostly eliminated via the kidney. Neither agencies establish a standard duration and frequency for sampling, it needs to be sufficient to correctly estimate PK parameters of the drug and metabolites. For drugs with high plasma protein binding, PK should be analyzed concerning to the unbound concentration of the drug and metabolites.

5.6. Measures of renal function

Renal function is assessed through Glomerular Filtration Rate (GFR). Both EMA and FDA agree that GFR is the best surrogate of renal function. However, agencies are not in agreement on how to determine GFR.

Firstly, EMA differentiate "measured GFR" and "estimated GFR" (eGFR). Measured GFR is referred to GFR assessed by an exogenous marker like inulin while eGFR is defined as GFR estimated by an endogenous marker which is not as accurate as measured GFR. GFR can also be calculated by urinary excretion of creatinine however, GFR could be overestimated because creatinine is also secreted, although in small quantities. EMA recommends the use of an exogenous marker to assess GFR in clinical studies, to have a reference measure independent of clinical practice. EMA also outlines that this is important, for example, for drugs that are supposed to be affected in a clinically relevant way that a dose adjustment will be needed. The use of an endogenous marker is not excluded. It can be used in special occasions like in a reduced-design study for hepatically eliminated drugs.

Conversely, FDA considers that creatinine clearance is the most practical method to evaluate renal function since is widely used in clinical practice. FDA acknowledges the use of the Cockcroft-Gault formula to estimate creatinine clearance from serum creatinine levels. Using other methods to determine renal function could lead to different characterization of GFR and may provide additional data about the effect of renal impairment on PK nevertheless, these methods cannot be used as alternatives creatinine clearance.

5.7. Dialysis

There is a significant number of patients on dialysis. In order to understand the impact of dialysis on the elimination process of the drug and to evaluate the need for dose adjustment or administration of supplementary dosing, a dialysis study is recommended. (Paglialunga *et al.*, 2017) A dialysis study also provides data about the value of dialysis for treatment of overdose.

EMA and FDA both outline that to understand the effect of dialysis, plasma PK should be assessed both at pre and post-dialysis conditions. According to FDA guidance, plasma protein binding should also be measured at both conditions. Agencies highlight that extrapolation of PK results at different models of dialysis can be ambiguous. The method likely to be used in the intended target population should be studied first. If an alteration on the PK parameters

is identified and is clinically relevant, PK studies on different methods of dialysis should be considered. The study can be omitted if the dialysis procedure is improbable to substantially affect PK parameters. FDA accepts that the dialysis study can be both integrated in the PK study or conducted as a separate study.

There are cases in which there is no need to study the effect of dialysis on drug clearance, as the drug is not expected to be largely affected by dialysis, due high protein binding or large volume of distribution.

5.8. Data analysis

Assessment of data from a PK study intend to determine, based on measured renal function, if dose adjustment is necessary for patients with decreased renal function and, if so, to recommend new dosing.

For EMA, estimation of PK parameters includes peak concentration, concentration over time curve (AUC) and half-life for all drugs and metabolites. For multiple-dose studies, minimum concentration should also be provided. Renal clearance should be estimated only if urinary excretion data was collected. FDA, besides the parameters required by EMA, also requires apparent clearance, renal clearance and apparent volume of distribution.

EMA guideline delineates how data should be presented while FDA does not have recommendations about this subject. According to EMA, relationship between renal function and PK parameters should be presented in graphical description, PK parameters related to renal function group should be presented by descriptive statistics and, geometric mean ratio for PK parameters in the group with most decreased renal function versus the control group should be used for reduced-design study.

5.9. Developing dosing recommendations

Dosing recommendations should be based on the results of the relationship between renal function and PK parameters.

EMA acknowledges that dosing recommendation should be based on absolute GFR and should be determined through a mathematical model, which supports calculations to identify the

correct dose and dosing intervals. Drug concentration must achieve a target range to demonstrate efficacy in patients with renal impairment. Strategies to reach the desirable concentration range can be reduction of the dose, prolonging dose interval or combine both. EMA outlines that to confirm the proposed dose recommendations, is necessary to perform simulations of the exposure in steady state. For drugs with narrow therapeutic index, EMA reflects on the need for therapeutic drug monitoring (TDM).

FDA also encourages the use of simulations to identify the optimal range of concentrations, doses and dosing interval for different renal function groups. Furthermore, FDA gives recommendations directly to sponsors related to the need for dose adjustment.

5.10. Concluding remarks

Available information regarding treatment of patients with renal impairment is limited because conducting clinical trials in these patients is challenging. Major difficulties when conducting a clinical trial in kidney disease are identifying a sufficient number of eligible patients that can be representative of the desire population, lack of study treatment compliance, complicated study design and inappropriate selection of outcomes resulting in lack of generalizability, recruitment failure and negative outcomes. Randomized clinical trials in renal impairment have lack of power which often leads to lack of efficacy and safety evidence about treatments. (Zhang *et al.*, 2012)

Guidelines from EMA and FDA describe when and how to conduct a PK study to properly develop dosing instructions for all renal impaired patients. Guidelines are similar both about study design and drug administration. However, methodology for GFR assessment differs from one agency to the other. It is necessary to standardize the technique that is used to evaluate the need for dose adjustment, otherwise results can differ from one method to another. More accurate methods and markers to measure kidney function in kidney dysfunction are needed because the ones describe in both guidelines suffer limitations and lack of accuracy. (Paglialunga *et al.*, 2017) Moreover, strategies to improve subjects' compliance to treatment need to be develop. Slightly differences in the determination of the renal function group can also lead to incorrect association between the group and the need for dose adjustment.

6. Conclusion

The growth of the number of patients with kidney disease is alarming. Therefore, social and economic consequences are significant and tend to increase.

Kidney diseases can cause several and sometimes unpredictable changes in all phases of drug pharmacokinetics: absorption, distribution, metabolism and excretion. Abnormalities apply not only to the parent drug but also to its metabolites. Each patient, with Acute Kidney Injury or with Chronic Kidney Disease, and each drug requires adequate therapeutic management with specific approaches to adjust dosage regimens. Erroneous adjustments may lead to too low or too high therapeutic concentrations and therefore to accumulation or sub-therapeutic effects. Either way, the patient can be predisposed to adverse effects or aggravate the disease state. One does not fit all. Adjustment of the dosage regimen depends on several factors at the same time: disease, cause of the disease, comorbidities, patient's characteristics, pharmacokinetics alterations and update reference sources.

Clinical guidelines and references are sets of recommendations to guide clinicians' decisions regarding prescription in patients with kidney disease. However, there is a large gap in the understanding of the effect on the pharmacokinetics of several commonly used drugs and hence on how to modify their dosage. Limited data, patients' inter-variability and disease heterogeneity difficult the development of new guidelines. Further research, studies and standards of care to improve renal patients' outcomes and life expectancy are most welcome.

This is the personalized medicine era. Therefore, efforts are already being made to discover and develop new possibilities for kidney care. Gene editing, bioengineering and new regulation for clinical research are ways to provide progress for kidney disease care and improve patients' quality of life.

References

AMERICAN KIDNEY FUND - Stages of Chronic Kidney Disease (CKD) [Consult. 30 jul. 2019]. http://www.kidneyfund.org/kidney-disease/chronic-kidney-disease-ckd/stages-of-chronic-kidney-disease/

ANDREW S. LEVEY, MD et al. - Annals of Internal Medicine Article Using Standardized Serum Creatinine Values in the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular. Annals of Internal Medicine. (2012).

ATKINSON, A. - EFFECTS OF RENAL DISEASE ON PHARMACOKINETICS. 3 (1999).

BENNETT, William - Drug prescribing in renal failure. Drugs. 17:2 (1979) 111–123.

BETTINGER, JJ et al. - Changes in pharmacokinetic parameters in patients with chronic kidney disease. (2016) 2014.

BLANCO, Victoria E. et al. - Acute Kidney Injury Pharmacokinetic Changes and Its Impact on Drug Prescription. (2019) 1–9.

BUGGE, J. F. - Pharmacokinetics and drug dosing adjustments during continuous venovenous hemofiltration or hemodiafiltration in critically ill patients. Acta Anaesthesiologica Scandinavica. (2001) 929–934.

CREWS, Deidra C. et al. - Burden, access, and disparities in kidney disease. Experimental and Clinical Transplantation. 17:2 (2019) 131–137.

DAVISON, Sara N. - Nephropharmacology for the Clinician Clinical Pharmacology Considerations in Pain Management in Patients with Advanced Kidney Failure. Clinical Journal of American Society of Nephrology. 14:6 (2019) 917–931.

DOOGUE, Matthew P.; POLASEK, Thomas M. - Doogue 2011 Drug Dosing in Renal Disease. 32:May (2011) 69–73.

Drug dosing consideration in patients with acute and chronic kidney disease - a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO) - https://www.kidney-international.org/article/S0085-2538(15)54984-3/fulltext

DW, Cockcroft; MH, Gault - Prediction of creatinine clearance from serum creatinine. Nephron. 16:1 (1976) 31–41.

EHRLICH, Paul - Address in Pathology ON CHEMOTHERAPEUTICS: The Lancet. 182:4694 (2003) 445–451.

FABRE, Jean; BALANT, L. - Renal Failure, Drug Pharmacokinetics and Drug Action. Clinical Pharmacokinetics. (1976) 99–120.

FACULTÉ DE BIOLOGIE ET DE MÉDICINE UNIVERSITÉ DE LAUSANNE - No Title [Consult. 30 jul. 2019]. https://sepia.unil.ch/pharmacology/?id=61

FAULL, Randall; LEE, Lisa - Prescribing in renal disease. Australian Prescriber. 30:1 (2007) 17–20.

GENOVESE, Giulio et al. - Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science. (2010) 841–845.

GIBALDI, Milo - Drug distribution in renal failure. The American Journal of Medicine. 62:4 (2004) 471–474.

GILBERT, Scott - National kidney foundation's primer on kidney diseases, sixth edition. ISBN 97814557461 70.

GONZALEZ, Frank; COUGHTRIE, Michael; TUKEY, Robert - The Pharmacological basis of therapeutics -Goodman & Gilman' s. ISBN 9780071769396.

HARTMANN, Bertram; CZOCK, David; KELLER, Frieder - Drug Therapy in Patients With Chronic Renal Failure. Deutsches Aerzteblatt Online. 107:37 (2010).

HASSAN, Yahaya et al. - Drug use and dosing in chronic kidney disease. Annals of the Academy of Medicine Singapore. 38:12 (2009) 1095–1103.

HON, Y. - Dose Adjustment in Renal and Hepatic Disease. Em EUROPE, MCGRAW-HILL EDUCATION- (Ed.) - Applied Biopharmaceutics & Pharmacokinetics. 7. ed. ISBN 978-0-07-183093-5. p. 1–43.

IBRAHIM, Rami B. et al. - Drug Removal by Plasmapheresis: An Evidence-Based Review. Pharmacotherapy. . ISSN 0277-0008. 27:11 (2007) 1529–1549. doi: 10.1592/phco.27.11.1529.

INTERNATION SOCIETY OF NEPHROLOGY - Kidney Health for Everyone Everywhere [Consult. 30 jul. 2019]. https://www.worldkidneyday.org/2019-campaign/2019-wkd-theme/

INTERNATIONAL SOCIETY OF NEPHROLOGY - Introduction to Acute Kidney Injury [Consult. 30 jul. 2019]. https://www.worldkidneyday.org/facts/topics/acute-kidney-injury/

INTERNATIONAL SOCIETY OF NEPHROLOGY - Global Kidney Health Atlas. www.theisn.org/global-atlas

JOGIA, Paresh; BRIEN, Matt - How to approach prescriptions for patients with renal impairment. Clinical Pharmacist. 1:4 (2009) 179–183.

JUNAID, Toluwalope et al. - Therapeutic Drug Monitoring. Em Clinical Pharmacy Education, Practice and Research. [S.l.] : Elsevier Inc., 2019 http://dx.doi.org/10.1016/B978-0-12-814276-9.00030-1

KDIGO - Clinical Practice Guideline for Acute Kidney Injury. Kidney International Supplements. 2:1 (2012) 1–138.

KDIGO - Clinical Practice Guidelines for Glomerulonephritis. Kidney International Supplements. 2:2 (2012) 139–274.

KDIGO - Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney International Supplements. 3:5 (2013) 419–475.

KERNS, Edward H.; DI, Li - Plasma Protein Binding Methods. Drug-like Properties: Concepts, Structure Design and Methods. (2009) 372–377.

KIDNEY DISEASE: IMPROVING GLOBAL OUTCOMES - Kidney Disease: Improving Global Outcomes Mission [Consult. 30 jul. 2019]. https://kdigo.org/mission/

KODNER, Charles - Diagnosis and Management of Nephrotic Syndrome in Adults. American family physician. 93:6 (2016) 479–85

LADDA, Matthew A.; GORALSKI, Kerry B. - The Effects of CKD on Cytochrome P450-Mediated Drug Metabolism. Advances in Chronic Kidney Disease. 23:2 (2016) 67–75.

LAGRUE, G. et al. - Proteinuria selectivity index: prognostic value in idiopathic nephrotic syndromes. Annales Med Interne (Paris) (1991).

LAM, Y. W. Franci. et al. - Principles of drug administration in renal insufficiency. Clinical Pharmacokinetics. 32:1 (1997) 30–57.

LAMATTINA, John; GOLAN, David - Princípios Fundamentais de Farmacologia. Em EDITORA GUANABARA KOOGAN S.A (Ed.) - Princípios de Farmacologia A Base Fisiopatológica da Farmacoterapia. p. 28–45

LEA-HENRY, Tom N. et al. - Nephropharmacology for the Clinician Clinical Pharmacokinetics

in Kidney Disease Fundamental Principles. Clinical Journal of American Society of Nephrology. 13:7 (2018) 1085–1095.

LECLRECQ, Marie-Paule; TULKENS, Paul - Aminoglycosides: Nephrotoxicity. Antimicrobial Agens and Chemotherapy. 43:5 (1999) 1003–1010.

LEO, Raphael J. - No TitleSafe Analgesic Use in Patients With Renal Dysfunction. (2014) [Consult. 30 jul. 2019]. https://www.practicalpainmanagement.com/treatments/pharmacological/safe-analgesic-use-patients-renal-dysfunction

LEVEY, Andrew S. et al. - PromoScience Eligability. Annals of Internal Medicine. ISSN 0003-4819. 2018). doi: 10.7326/0003-4819-150-9-200905050-00006.

LEVEY, Andrew S.; LEVIN, Adeera; KELLUM, John A. - Definition and Classification of Kidney Diseases. American Journal of Kidney Diseases. (2013) 686–688.

LOO, Dean A. Van; DOWLING, Thomas C. - Renal Drug Dosing Concepts. Em Clinical Pharmacokinetics, https://www.ashp.org/-/media/store-files/p5365-sample-chapter.ashx

LUYCKX, Valerie A.; TONELLI, Marcello; STANIFER, John W. - The global burden of kidney disease and the sustainable development goals. Bulletin of the World Health Organization. 96:6 (2018) 414-422C.

MAKRIS, Konstantinos; SPANOU, Loukia - Acute Kidney Injury: Definition, Pathophysiology and Clinical Phenotypes. 37:2 (2016) 85–98.

MCAINSH, J. et al. - Atenolol kinetics in renal failure. Clinical Pharmacology & Therapeutics. (1980) 302–309.

MCINTYRE, Christopher W.; SHAW, Susan; ELDEHNI, Mohamed T. - Prescribing Drugs in Kidney Disease. Em Brenner and Rector's The Kidney. p. 2258–2291.

NICHOLSON, J. P.; WOLMARANS, M. R.; PARK, G. R. - REVIEW ARTICLE The role of albumin in critical illness. British Journal of Anaesthesia. 85:4 (2000) 599–610.

NOLIN, Thomas D. - A Synopsis of Clinical Pharmacokinetic Alterations in Advanced CKD. Seminars in Dialysis. 28:4 (2015) 325–329.

PAGLIALUNGA, Sabina et al. - Update and trends on pharmacokinetic studies in patients with impaired renal function: practical insight into application of the FDA and EMA guidelines. Expert Review of Clinical Pharmacology. 10:3 (2017) 273–283.

PHILIPS, Barbara J. et al. - The effects of acute renal failure on drug metabolism. Expert Opinion on Drug Metabolism & Toxicology. 10:1 (2014) 11–23.

POTTEL, Hans et al. - An estimated glomerular filtration rate equation for the full age spectrum. Nephrology Dialysis Transplantation. 31:5 (2016) 798–806.

RICHARD, J JOHNSON; JOHN, Feehally; Jürgen; FLOEGE - Comprehensive Clinical Nephrology 5th Edition. ISBN 9780874216561.

ROBERTS, Darren M. et al. - Clinical pharmacokinetics in kidney disease application to rational design of dosing regimens. Clinical Journal of the American Society of Nephrology. 13:8 (2018) 1254–1263.

ROBLES-OSORIO, L.; SABATH, Ernesto - Social disparities, risk factors and chronic kidney disease. Elsiever España. 6:5 (2016) 577–579.

ROSTOKER, Guy et al. - Accuracy and limitations of equations for predicting the glomerular filtration rate during follow-up of patients with non-diabetic nephropathies. BMC Nephrology. 10:1 (2009) 1–10.

SCOTT, Ian A. et al. - Reducing inappropriate polypharmacy: The process of deprescribing. JAMA Internal Medicine. 175:5 (2015) 827–834.

SHANNON, Michael W. - Comparative efficacy of hemodialysis and hemoperfusion in severe theophylline intoxication. Academic Emergency Medicine. 4:7 (1997) 674–678.

SHIRAZIAN, Shayan; RADHAKRISHNAN, Jai - Gastrointestinal disorders and renal failure: Exploring the connection. Nature Reviews Nephrology. 6:8 (2010) 480–492.

SIDDALL, Eric C.; RADHAKRISHNAN, Jai - The pathophysiology of edema formation in the nephrotic syndrome. Kidney International. 82:6 (2012) 635–642.

SMYTH, Brendan; JONES, Ceridwen; SAUNDERS, John - Prescribing for patients on dialysis. Australian Prescriber. 39:1 (2016) 21–24.

STEVENS, Lesley A. et al. - Assessing Kidney Function — Measured and Estimated Glomerular Filtration Rate. New England Journal of Medicine. 354:23 (2006) 2473–2483.

TAYLOR, Maria E.; ALLON, Michael - Practical Vancomycin Dosing in Hemodialysis Patients in the Era of Emerging Vancomycin Resistance: A Single-Center Experience. American Journal of Kidney Diseases. 55:6 (2010) 1163–1165.

TENCER, Jan; BAKOUSH, Omran; TORFFVIT, Ole - Diagnostic and prognostic significance of proteinuria selectivity index in glomerular diseases. Clinica Chimica Acta. 297:1–2 (2000) 73–83.

THOMAS, David M.; COLES, Gerald A.; WILLIAMS, John D. - What does the renal reserve mean? Kidney International. 45:2 (1994) 411–416.

THOMPSON, Stephanie et al. - Cause of Death in Patients with Reduced Kidney Function. Journal of the American Society of Nephrology. 26:10 (2015) 2504–2511.

TOZER, T. N.; ROWLAND, M. - Introduction to Pharmacokinetics and Pharmacodynamics: The Quantitative Basis of Drug Therapy

U.S. FOOD AND DRUG ADMINISTRATION - FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function. (2017) [Consult. 30 jul. 2019]. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-revises-warnings-regarding-use-diabetes-medicine-metformin-certain

U.S. FOOD AND DRUG ADMINISTRATION - Route of Administration. (2018) [Consult. 30 jul. 2019]. https://www.fda.gov/industry/structured-product-labeling-resources/route-administration

UNITED NATIONS - United Nations - Overview [Consult. 30 jul. 2019]. https://www.un.org/en/sections/about-un/overview/index.html

UNIVERSITY OF NOTTINGHAM - Drug Elimination [Consult. 30 jul. 2019]. https://www.nottingham.ac.uk/nursing/sonet/rlos/bioproc/kidneydrug/page_one.html

VERBEECK, Roger K.; MUSUAMBA, Flora T. - Pharmacokinetics and dosage adjustment in patients with renal dysfunction. European Journal of Clinical Pharmacology. 65:8 (2009) 757–773.

WEBSTER, Angela C. et al. - Chronic Kidney Disease. The Lancet. 389:10075 (2017) 1238–1252.

WHITTAKER, Chanel F. et al. - Medication safety principles and practice in CKD. Clinical Journal of the American Society of Nephrology. 13:11 (2018) 1738–1746.

WORLD HEALTH ORGANIZATION - The top 10 causes of death (2018) [Consult. 30 jul. 2019]. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

ZHANG, Lei et al. - Regulatory Perspectives on Designing Pharmacokinetic Studies and Optimizing Labeling Recommendations for Patients With Chronic Kidney Disease. The Journal of Clinical Pharmacology. 52:S1 (2012) 79S-90S.