ELVINA MOSER

ANALYSIS OF DIFFERENCES IN AUGMENTED RENAL CLEARANCE CASES AND THEIR RELEVANCE TO PHARMACOKINETICS

Master’s thesis

KAUNAS, 2014
ANALYSIS OF DIFFERENCES IN AUGMENTED
RENAL CLEARANCE CASES AND THEIR
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Master's thesis

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SUMMARY

Master Thesis of E. Moser “Analysis of Differences in Augmented Renal Clearance cases and their relevance to pharmacokinetics“, supervisor Prof. R. Mačiulaitis;

Lithuanian University of Health Sciences, Academy of Medicine, Faculty of Pharmacy, Institute of Physiology and Pharmacology – Kaunas, 2014

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Objective of the work: The purpose of this quantitative retrospective comparative study was to register possible cases of augmented renal clearance (ARC) in patients of Hospital of Lithuanian University of Health Sciences and analyse the differences in assessments of cases of Augmented Renal Clearance and the drug therapy problems related to ARC.

Tasks: To achieve the objective, several tasks were performed: 1) to register possible ARC patients cases as assessed by Cocroft-Gault and their possible associated reasons; 2) to analyse differences in three equations used for GFR estimation: Cocroft-Gault, MDRD simplified, and CKD-EPI. 3) compare the therapies of the patients and determine the drugs that are in risk of being underdosed when ARC is present.

Methodology: An ARC survey (appendix 1) was filled about patients from various departments of Clinics during the period of 2013 03 04 – 2014 08 15. All patients were selected according serum creatinine values that were 50 µmol/l. or less. Two groups of patients were assigned for analysis: patients were grouped according Cocroft-Gault creatinine clearance values: (1) ARC group A CrCl >130 ml./min and (2) comparative Non-ARC group B CrCl 90-130 ml./min. Data were analyzed by using descriptive and comparative statistical analysis, considering statistically significant difference between the groups if p value was <0.05.

Results and conclusions:
1. In the research group and comparative groups were 31 patients selected (totally 62 patients). Based on the study results can be concluded that ARC (when glomerular filtration rate 130ml/min. and more) assessed by Cocroft-Gaul equation was not sufficiently replicated by CKD-EPI. In Non-ARC patients (when glomerular filtration rate is 90 -130 ml/min.), the absence of ARC was not sufficiently replicated by MDRD formula.

2. ARC was detected almost equally in the ICU (as expected), non-ICU surgical and non-ICU therapeutic departments.

3. The ARC-patients had several possible known risk factors, most frequently it was “young age” (below 60 years), surgery and trauma followed by less frequent risk factors as diabetes and pancreatitis. It is specifically remarkable that “young age”, which is usually meant to be associated with good health, increases the risk of ARC and therefore the risk of underdosing renally excreted drugs.

4. Most of the patients with ARC received only renally excreted drugs dosed at minimal doses. Mostly taken drugs were cefuroxim, fraxiparin, ranitidine, ketoprofen followed by less frequently taken metoprolol, gentamycine, furosemide.

**Key words:** Augmented renal clearance, ICU, pharmakokinetics, GFR, subtherapeutic dosing.
INTRODUCTION

In recent years, the focus on augmented renal clearance increased as it was found by some researchers (A.Udy et al., 2010; J.Baptista et al., 2011; A.Roberts et al., 2013 and U.Tröger et al., 2012) that this condition results in subtherapeutic drug dosing concentrations. Accurate assessment of renal function is important for prescribing optimal dosis of pharmaceuticals for ARC patients.

To identify ARC there are different ways of estimating renal function and one of the mostly used is Glomerular filtration rate estimation. Of course GFR can be also calculated directly, but as it is very time-consuming and costly procedure there are different formulas applied to make GFR estimation more convenient and available in clinical practice.

This study compares GFR estimations of the patients using three different equations: Cocroft-Gault, MDRD and CKD-EPI.

There were several studies made to compare for GFR estimation used formulas (Grubb et al., Levey et al., Verhave et al.) but none of them compared three different GFR estimation formulas at the same time. There was a study which compared Cocroft-Gault and MDRD simplified and complex MDRD formulas. (Kuzmickis et al.)

Even though this study is comparatively small (only 31 patient in ARC and 31 in comparative group) it hopefully will help for better understanding of ARC phenomenon, especially its possible associated reasons and relevance to pharmacokinetics and will encourage future research in this topic.
ABBREVIATIONS

ARC: augmented renal clearance
CrCl: creatinine clearance
CKD: a progressive loss in renal function over a period of months or years
GFR: glomerular filtration rate
ICU: intensive care unit
Scr: serum creatinine
MDRD: Modification of diet in renal disease
MODS: Multiorgan dysfunction syndrome
DEFINITIONS

Augmented renal clearance: enhanced renal elimination of circulating solutes such as waste products or pharmaceuticals when CrCl ≥130 ml/min.

Anthropometric values: specific dimensions of the body, such as height and weight.

Creatinine clearance: is the volume of blood plasma that is cleared of creatinine per unit time and is a useful measure for approximating the GFR.

Glomerular filtration rate: flow rate of filtered fluid through the kidney.

Intensive care unit: a special department of a hospital or health care facilities that is dedicated to manage critically ill patients.

Multiorgan dysfunction syndrome: is altered organ function in an acutely ill patient requiring medical intervention to achieve homeostasis.
TASKS AND OBJECTIVES OF THE WORK

The aim of this study was to analyse the differences in drug effects in patients with ARC of Hospital of Lithuanian University of Health Sciences Kaunas Clinics.

Tasks:

1. To register possible cases of Accelerated renal clearance in patients of Hospital of Lithuanian University of Health Sciences and determine their possible reasons.

2. Analyse differences in three for GFR estimation used formulas: Cocroft-Gault, MDRD and CKD-EPI.

3. To compare therapies in ARC and Non-ARC groups and determine the risk drugs for changed renal elimination.
1. THEORETICAL BACKGROUND

1.1. Augmented renal clearance definition

Augmented renal clearance (ARC) became object of many studies in the last few years. This state can be defined as „enhanced renal elimination of circulating solutes (such as waste products or pharmaceuticals), and is quantified by the volume of plasma cleared of a given substance by the kidneys per unit of time ml/min.“. ARC is important especially for critically ill patients as they are in risk of suboptimal drug doses and treatment failure.¹ As Carlier et al. describes, ARC occurs due to pathophysiological changes and the incidence of ARC in critically ill patients is between 30-85% depending on the studied population and the definition of ARC.² In Europe accepted definition of ARC corresponds with Creatinine clearance values equal or greater than 130 ml/min. (CrCl≥130 ml/min.)

According to one of the last years study „ARC is mostly described in critically ill patients in the Intensive Care Unit (ICU) with various incidence rates and no universally accepted aetiology“.³

1.2. Functions of the kidney

The right kidney sits just below the diaphragm and posterior to the liver, the left below the diaphragm and posterior to the spleen. Resting on top of each kidney is an adrenal gland. The upper (cranial) parts of the kidneys are partially protected by the eleventh and twelfth ribs, and each whole kidney and adrenal gland are surrounded by two layers of fat (the perirenal and pararenal fat) and the renal fascia. Each adult kidney weighs between 125 and 170 grams in males and between 115 and 155 grams in females. The substance, or parenchyma, of the kidney is divided into two major structures: superficial is the renal cortex and deep is the renal medulla. Grossly, these structures take the shape of 8 to 18 cone-shaped renal lobes, each containing renal cortex surrounding a portion of medulla called a renal pyramid (of Malpighi)⁴.

¹ Udy A.A. et al., 2010
² Carlier et al.
³ Minkutė, R., et al 462-467
⁴ Walter F.
To understand the importance of ARC we first need to understand how the kidney functions. The main function of the kidney is excretion of circulating metabolites, toxins and drug substances. Excretion is combined process that consists of glomerular filtration, tubular secretion and reabsorption.\textsuperscript{5}

Between the renal pyramids are projections of cortex called renal columns (of Bertin). Nephrons, the urine-producing functional structures of the kidney, span the cortex and medulla. The initial filtering portion of a nephron is the renal corpuscle, located in the cortex, which is followed by a renal tubule that passes from the cortex deep into the medullary pyramids. Part of the renal cortex, a medullary ray is a collection of renal tubules that drain into a single collecting duct\textsuperscript{6}.

Figure 1. How kidney work: the mechanism
(http://www.mhhe.com/biosci/esp/2001_gbio/folder_structure/an/m9/s4/)

Kidney also serve homeostatic functions such as the regulation of electrolytes, maintenance of acid–base balance, and regulation of blood pressure (via maintaining salt and

\textsuperscript{5}Udy A.A. et al., 2010
\textsuperscript{6}Clapp, WL.
water balance). They serve the body as a natural filter of the blood, and remove water soluble wastes.  

In case of ARC, these kidney functions are altered compared to expected base line and it further results in accelerated drug substance excretion. The speed of drug substance excretion is crucial for setting a successful drug dosage regimen.

### 1.3. Glomerular filtration rate

Glomerular filtration rate (GFR) describes the flow rate of filtered fluid through the kidney. Creatinine clearance rate (CCr or CrCl) is the volume of blood plasma that is cleared of creatinine per unit time and is a useful measure for approximating the GFR. Creatinine clearance exceeds GFR due to creatinine secretion, which can be blocked by cimetidine. In alternative fashion, overestimation by older serum creatinine methods resulted in an underestimation of creatinine clearance, which provided a less biased estimate of GFR.

To estimate glomerular filtration rate is important for several reasons: either it is renal disease evaluation, setting drug dosage regimen or evaluating renal involvement in some systemic diseases like diabetes melitus. It is important to understand that creatinine is also dependent on muscle mass, age and gender which means that creatinine based GFR calculation might not always be reliable. According to Udy et al. the best ways to measure the GFR are inulin or iohexol clearance, and radionucleotide studies. Even though these tests provide the most accurate results, they are not widely available in clinical setting.

### 1.4. Creatinine – based glomerular filtration rate approximations

#### 1.4.1. Markers of renal function tests

Urea, uric acid, electrolytes, cystatin C and β-Trace Protein all are markers for renal function tests but serum creatinine value is the most commonly used marker in practice.

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7 Robins and Cotran, p.910  
8 Stevens L.A.  
9 Gockcroft DW.
According the definition „Creatine is a breakdown product of creatine phosphate in muscle, and is usually produced at a fairy constant rate by the body depending on muscle mass“.

Botev et.al. concludes that glomerular filtration rate (GFR) has a paramount diagnostic and staging role for kidney disease patients and is the best index of renal function. Very often used serum creatinine-based formulas in adults for estimated GFR are the Cockroft-Gault (CG) and Modification of Diet in Renal Disease Study (MDRD).

1.5. Creatinine clearance

Clearance is a function of glomerular filtration, secretion from the peritubular capillaries to the nephron, and reabsorption from the nephron back to the peritubular capillaries. Clearance is constant in first-order kinetics because a constant fraction of the drug is eliminated per unit time, but it is variable in zero-order kinetics, because the amount of drug eliminated per unit time changes with the concentration of the drug in the blood.

The creatinine clearance test is used to estimate glomerular filtration rate (GFR). GFR is a measure of how well the kidneys are working, especially the kidneys’ filtering units. These filtering units are called glomeruli. Creatinine is removed, or cleared, from the body entirely by the kidneys. If kidney function is abnormal, creatinine level increases in the blood because less creatinine is released through the urine.

The reatinine clearance (CrCl) is considered the most practical marker for determining the glomerular filtration rate. One of the methods of creatinine clearance estimation is 24-hour urine collection coupled with a serum creatinine measurement. The rate of excretion is calculated by comparing amount of creatinine n plasma to the amount of creatinin in urine over a period of 24 hours. This is one of the ways CrCl can be calculated and it is unfortunatelley not very often applied in practice because of the practical difficulties (e.g. difficulty to collect urine 24-hours) of this approach. A much more practical way of determining CrCl is estimating the rate of production of creatinine vs. estimating the rate of elimination as it is done in former method. To estimate the rate of production it takes only

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12 Yuegang Z.
13 Botev et al.
14 Kaplan
14 Israni AK.
single measure of serum creatinine. After serum creatinine measure is taken (blood sample is taken to determine serum creatinine) CrCl using different equations can be calculated.\textsuperscript{15} 

Clearance is often measured as milliliters/minute (ml/min). Normal values are\textsuperscript{16}:

- Male: 97 to 137 ml/min.
- Female: 88 to 128 ml/min.

Normal value ranges may vary slightly among different laboratories. Some labs use different measurements or test different samples. Talk to your doctor about the meaning of your specific test results. What Abnormal Results Mean. Abnormal results (lower than normal creatinine clearance) may indicate\textsuperscript{17}:

- Kidney problems, such as damage to the tubule cells;
- Kidney failure;
- Too little blood flow to the kidneys;
- Damage to the filtering units of the kidneys;
- Loss of body fluids (dehydration);
- Bladder outlet obstruction;
- Heart failure.

Based on several papers and expert opinions, now provide adjustments to the Cockcroft-Gault equation based on body weight and BMI, as it appears to become less accurate in weight extremes (underweight and particularly overweight/obesity). As recommended by Brown et. al and Winter et. al, we provide adjustments and estimates as follows\textsuperscript{18}:

- Underweight (BMI < 18.5): Weight uses actual/total body weight (No adjustment).
- Normal Weight (BMI 18.5 - 22.9): Weight uses ideal body weight (with the range using the actual body weight).
- Overweight/Obese (BMI ≥ 23): Weight uses adjusted body weight (with the range using ideal body weight).

\textsuperscript{15} Walker, R.
\textsuperscript{16} McPherson RA.
\textsuperscript{17} Israni AK.
\textsuperscript{18} Brown DL. P.105
1.6. Cockroft-Gault equation

In 1976, Cockcroft and Gault introduced a equation comprising several anthropometric variables. Anthropometric values included in the formula were gender, age, weight and they help compensate for the inadequacies of creatinine level as a marker of glomerular filtration rate (GFR). 19

Derivation included the relationship found between age and 24-hour creatinine excretion/kg in 249 patients aged 18–92. Values for Ccr were predicted by this formula measured in 236 patients. The formula gave a correlation coefficient between predicted and mean measured Ccr·s of 0.83; on average, the difference between predicted and mean measured values was no greater than that between paired clearances. 20

\[
\text{GFR (mL/min/1.73 m}^2\text{)} = \frac{(A \times (140 - \text{age}) \times \text{weight})}{\text{Cre}}
\]

Where A: 1.23 for male , 1.04 for female

Formula 1. Cockroft-Gault equation

The advantage of this approach is that the time-consuming and error-biased collection of 24 hour urine can be skipped, whereas the results are of similar quality.

The weakness of this approach is that it tends to be imprecise especially in cases of acute renal failure, instable renal function, strong edema or adipositas. 21

1.7. Modification of diet in renal disease equation (MDRD)

The abbreviated Modification of Diet in Renal Disease (MDRD) study equation [was derived from Caucasians and African Americans with chronic kidney diseases (CKD) and is not accurate for Asians or when the estimating equations for glomerular filtration rate (eGFR) are above 60 mL/min/1.73 m2. Thus, some Asian countries have developed their own eGFR equations.,. However, many equations were derived solely from CKD patients, thereby having limitations in application to the general population. For example, the MDRD equation

19 Grubb A. Et al.
20 Cockcroft D.W.
21 cf: http://www.bioscientia.de/de/service/medizinische-formeln/gfr_nach_cockgroft_gould/#
underestimated the gold standard GFR measured by inulin clearance (Cin) for those with Cin of greater than 60 mL/min/1.73 m² in a recent Japanese study²².

The most commonly used equation is the Modification of Diet in Renal Disease (MDRD) Study equation. There is now a considerable body of literature demonstrating variation in performance of these equations among study populations²³.

In part, this variation is due to differences among studies in range of GFR, methods for GFR measurement, and serum creatinine assays. We pooled individual patient data from six research studies and four clinical populations, with similar GFR measurements protocols and serum creatinine assays calibrated to a reference standard, to describe the performance of the MDRD Study equation, with particular attention to the level of GFR and participant clinical characteristics²⁴.

This equation was created to simplify prediction of GFR and included only demographic and serum variables. Independent factors associated with a lower GFR included a higher serum creatinine concentration, older age, female sex, nonblack ethnicity, higher serum urea nitrogen levels, and lower serum albumin levels²⁵. The strength of this formula is a higher accuracy because of respecting more GFR-relevant factors of the patient.

The Equation was developed in 1999 by Levey et al. was meant to replace the commonly used Cockroft-Gault equation, but did not gain much success in practice. „The principal objective of MDRD was to study the effect of dietary protein restriction and strict BP control on the progression of chronic kidney disease (CKD)”²⁶. Several studies reported that MDRD formula underestimates GFR in patients who do not have renal disease²⁷.

Additionally, it might lead to erroneous results and should therefore be avoided in these patient groups: children under, pregnant women, extreme muscle mass (bodybuilder), extraordinary length of body, quickly changing renal function, overweight, underweight, vegetarian diet²⁸.

According Verhave et al who studied 850 patients, GFR estimation while using MDRD was about 10% underestimated²⁹.

²² Ling-I Chen, Jinn-Yuh Guh.
²⁴ Stevens L.A., Coresh J.
²⁵ Levey AS,461-470.
²⁶ Andrew S., et al.
²⁷ Mai T. Et al.
²⁸ http://www.bioscientia.de/de/service/medizinische-formeln/gfr_mdrd/#
²⁹ Verhave JC.
GFR (mL/min/1.73 m^2) = 175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times A

A: 0.742 if female or 1.212 if African American

**Formula 2. Modification of diet in renal disease equation (MDRD)**

These formulas contain common variables such as age, body weight, gender, serum creatinine, and albumin blood urea nitrogen levels. In February 2002, the Kidney Disease Outcome Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF) published clinical practice guidelines for chronic kidney disease. This guideline suggested that the Modification of Diet in Renal Disease (MDRD) formula and the Cockcroft Gault (CG) formula provide useful estimates of the GFR (eGFR) in adult patients. Some studies suggested that the results of CG formula is closer to 125I-iothalamate renal clearance than the results of MDRD formula in individuals with advanced kidney disease. However, there are growing doubts about the accuracy of CG formula in individuals with normal renal function. Despite the arguments, the CG formula is one of the most commonly used formulas.30

According to the scientists' calculations, studies suggest, that the differences between the MDRD and CG formula were not only influenced by age, body mass index and serum creatinine but also affected by gender, hypertension, and diabetes. In clinical practice, physicians should be aware of these differences and take them into consideration when they estimate renal functions.31

**1.8. Chronic kidney disease epidemiology collaboration equation (CKD-EPI)**

In May 2009 a Chronic Kidney Disease Epidemiology collaboration formula was published with the expectation of more accurate GFR estimation possibilities. Instead of creatinine, this formula focuses on the filtration of cystatin C. The formula is superior in accuracy especially for patients in first stage of impaired renal function. Even though this formula showed decrease in bias it remained imprecise. The coefficients in the formula represent average effects observed in the population used to

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develop the equations and exclude patients at the extremes of muscle mass (including frail elderly, critically ill, or cancer patients), those with unusual diets, and those with conditions associated with reduced secretion or extra-renal elimination of creatinine.  

\[
GFR = 141 \times \min(\text{Scr}/\kappa,1)^{\alpha} \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}}
\]

where: \( X 1.018 \) [if female] \( X 1.159 \) [if black]

**Formula 3.** Chronic kidney disease epidemiology collaboration CKD-EPI equation

\[\text{GFR} = 141 \times \min(\text{Scr}/\kappa,1)^{\alpha} \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}}\]

where: \( X 1.018 \) [if female] \( X 1.159 \) [if black]

**Figure 1.** Accuracy of the CKD-EPI and MDRD equations to estimate GFR for the validation data set (N=3896). Both panels show the difference between measured and estimated (y-axis) vs. estimated GFR (x-axis).  

1.9. Normal GFR values

According UK Renal Association, GFR over 90 ml/min 1.73 m\(^2\) is normal unless there is other any evidence of kidney disease. In case GFR is less than 90 ml/min 1.73 m\(^2\), patient might be diagnosed with I degree chronic kidney disease (CKD).  

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\[32\text{Stevens LA, 449}\]
\[33\text{From Annual Internal Medicine Journal 2009;150:604-612,}\]
\[34\text{British kidney association website: http://www.britishkidney-pa.co.uk/patient-info}\]
Values of kidney function tend to differ from particular population and individuals so it is difficult to accurately define the process. Normal (GFR) values are about 130 ml/min. in young women and men. It is important to mention that these values decline with increasing age.

In the table below, the normal values of GFR (ml/min) are grouped according the gender and age parameters, calculated using Cockroft-Gault formula:

<table>
<thead>
<tr>
<th>Age</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 - 29</td>
<td>72 - 100</td>
<td>94 - 140</td>
</tr>
<tr>
<td>30 - 39</td>
<td>71 - 121</td>
<td>59 - 137</td>
</tr>
<tr>
<td>40 - 49</td>
<td>50 - 102</td>
<td>76 - 120</td>
</tr>
<tr>
<td>50 - 59</td>
<td>50 - 98</td>
<td>67 - 109</td>
</tr>
<tr>
<td>60 - 69</td>
<td>45 - 75</td>
<td>54 - 98</td>
</tr>
<tr>
<td>70 - 79</td>
<td>37 - 61</td>
<td>49 - 79</td>
</tr>
<tr>
<td>From 80</td>
<td>27 - 55</td>
<td>30 - 60</td>
</tr>
</tbody>
</table>

Table 5. From: Thomas L., Labor und Diagnose

One study reports that Cockroft-Gault formule for indirect estimation of GFR does not give precise results, this formula going to be used in this study because unavailability of other better GFR estimation methods.

1.10. Possible reasons of ARC

36 Thomas L.
37 Kuzminskis V. et al.
As ARC is comparatively new phenomenon, not many studies and researches have been made to find out the possible reasons of it.

Researcher Andrew Udy made several studies in this topic and as possible associated ARC reasons excluded:

1. Younger Age (<60 years).
2. Pregnancy.
3. Sepsis.
4. Trauma.
5. Surgery or neurosurgery.
8. Cystic fibrosis.

These eight possible associated reasons of ARC have not been extensively studied and could become a topic of future research.

1.11. Setting an appropriate dosage regimen for the ARC patients

Most of drug dosing regimens derive from data that is taken from healthy volunteers. Ill patients that have different pathophysiology than healthy ones and require different dosing schedules.

ARC patients are the ones that are mostly in need for better adjusted therapeutic dosage regimen, because:

1. patients with ARC have increased GFR, which means renally excreted drugs are excreted faster than normal without fully exerting their effect, which strongly indicates for dosage adjustment;

2. even though therapeutic drug monitoring (TDM) is more often available, case studies report that subtherapeutic doses of β-lactam antibiotics, especially meropenem, have been detected in 48% of the patients and even 80% of them had ARC.\(^{38}\)

Study made by Baptista J. et al.(2011) associated ARC with subtherapeutic serum vancomycin concentrations, especially on the first three days of treatment period.\(^{39}\)

\(^{38}\)Carlier M. et al.
\(^{39}\)Baptista J. et al. p.420
case study made by Tröger U. et al. concluded that patients with present ARC needed much higher meropenem dosages compared to empirical dosage regimen. \(^{40}\)

### 1.12. Only renally excreted drugs

Most of drugs are renally excreted. Drugs that are excreted mainly renally are in the main risk to fail in reaching therapeutic dosages of ARC patients. It is important to detect such drugs in ARC patients’ prescriptions and consider possible dosage changes for these drugs. Some of such drugs are: penicillins, cephalosprins, aminoglycosides, tetracycline, ranitidine, cimetidine, porcainamide, digoxin, lithium, diuretics, gentamicine, beta blockers. \(^{41}\)

Renal filtration accounts for most drug excretion. About one fifth of the plasma reaching the glomerulus is filtered through pores in the glomerular endothelium; nearly all water and most electrolytes are passively and actively reabsorbed from the renal tubules back into the circulation. However, polar compounds, which account for most drug metabolites, cannot diffuse back into the circulation and are excreted unless a specific transport mechanism exists for their reabsorption (eg, as for glucose, ascorbic acid, and B vitamins). With aging, renal drug excretion decreases; at age 80, clearance is typically reduced to half of what it was at age 30 \(^{42}\).

Renal disease interacts with drugs in three main ways. Firstly, patients with renal disease may be more vulnerable to a given drug effect (patient susceptibility). Secondly, a drug effect may be exaggerated or attenuated in patients with renal disease (pharmacodynamic change). Thirdly, and most important, some drugs have higher steady-state concentrations when given at usual doses to patients with renal disease (pharmacokinetic changes). \(^{43}\)

The following table (see Table 6) shows which products of the drug are in risk decreased renal or hepatic elimination with increasing age.

<table>
<thead>
<tr>
<th>Class or Category</th>
<th>Decreased Hepatic Metabolism</th>
<th>Decreased Renal Elimination</th>
</tr>
</thead>
</table>

\(^{40}\)Tröger U. et al.

\(^{41}\)http://www.gpnotebook.co.uk/simplepage.cfm?ID=-1321926612

\(^{42}\)Mark Ruscin

\(^{43}\)Doogue M.P.
<table>
<thead>
<tr>
<th>Analgesics and anti-inflammatory drugs</th>
<th>Ibuprofen</th>
<th>Meperidine</th>
<th>Meperidine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Morphine</td>
<td></td>
<td>Morphine</td>
</tr>
<tr>
<td></td>
<td>Naproxen</td>
<td></td>
<td>Oxycodone</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>-</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Amikacin</td>
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<td></td>
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<tr>
<td></td>
<td>Ciprofloxacin</td>
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<tr>
<td></td>
<td>Gentamicin</td>
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<td></td>
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<td></td>
<td>Levofloxacin</td>
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<td></td>
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<tr>
<td></td>
<td>Nitrofurantoin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Streptomycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tobramycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular drugs</td>
<td>Amlodipine</td>
<td></td>
<td>$N$-Acetylprocainamide</td>
</tr>
<tr>
<td></td>
<td>Diltiazem</td>
<td></td>
<td>Apixaban</td>
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<tr>
<td></td>
<td>Lidocaine</td>
<td></td>
<td>Captopril</td>
</tr>
<tr>
<td></td>
<td>Nifedipine</td>
<td></td>
<td>Dabigatran</td>
</tr>
<tr>
<td></td>
<td>Propranolol</td>
<td></td>
<td>Digoxin</td>
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<tr>
<td></td>
<td>Quinidine</td>
<td></td>
<td>Enalapril</td>
</tr>
<tr>
<td></td>
<td>Theophylline</td>
<td></td>
<td>Enoxaparin</td>
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<tr>
<td></td>
<td>Verapamil</td>
<td></td>
<td>Heparin</td>
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<tr>
<td></td>
<td>Warfarin</td>
<td></td>
<td>Lisinopril</td>
</tr>
<tr>
<td>Diuretics</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amiloride</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Furosemide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Triamterene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychoactive drugs</td>
<td>Alprazolam</td>
<td></td>
<td>Risperidone</td>
</tr>
<tr>
<td></td>
<td>Chlordiazepoxide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Desipramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diazepam</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Imipramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nortriptyline</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trazodone</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Triazolam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Levodopa</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amantadine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chlorpropamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cimetidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exenatide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gabapentin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glyburide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lithium</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metoclopramide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ranitidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sitagliptin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 6. List of pharmaceutical drugs that are in risk of decreased renal or hepatic elimination with increasing patients age. 44

Renal disease alters the effects of many drugs, particularly when active drug moieties are renally cleared. Drug doses should usually be reduced in renal disease in proportion to the predicted reduction in clearance of the active drug moiety. Patient factors to consider in adjusting drug doses include the degree of renal impairment and patient size. Drug factors to consider in adjusting doses include the fraction of the drug excreted unchanged in urine and the drug’s therapeutic index. Estimates of renal function are useful to guide dosing of renally cleared drugs with medium therapeutic indices, but are not precise enough to guide dosing of drugs with narrow therapeutic indices. 45.

1.13. Drug dosage adjustment for ARC patients

According to the researchers dosages of drugs cleared renally should be adjusted according to creatinine clearance or glomerular filtration rate and should be calculated using online or electronic calculators. Recommended methods for maintenance dosing adjustments are dose reductions, lengthening the dosing interval, or both. Physicians should be familiar with commonly used medications that require dosage adjustments. Resources are available to assist in dosing decisions for patients with chronic kidney disease46.

Optimal antimicrobical use in MODS in complex and dependent on drug-, disease- and patient-related factors. The contribution of an ICU pharmacist to optimization of antimicrobial use can be manifested in the provision of advise on dose adjustments that consider drug physicochemical and pharmacodynamic characteristics as well as disease-related alterations in antimicrobial pharmacokinetics47.

Thus the usual dosage regimen of a drug interaction on drug can often be adjusted quantitatively to a new regimen in these abnormal conditions in order to maintain the desired therapeutic blood concentration level of the pharmacologic agent. The dosage regimen for a drug is usually made up of the initial or „loading“ dose, which is intended to „fill“ the body with the given drug concentration at periodic intervals in order to sustain the therapeutic

44 JMark Ruscin.
45 Doogue M.P.
46 Myrna Y.
47 Rello J., Lipman J.
level\textsuperscript{48}. According to the authors Myrna, Munar, Pharmd, dosing adjustments: dose reduction, lengthening the dosing interval, or both. Dose reduction involves reducing each dose while maintaining the normal dosing interval. This approach maintains more constant drug concentrations but it is associated with a higher risk of toxicities if the dosing interval is inadequate to allow for drug elimination. Normal doses are maintained with the extended interval method, but the dosing interval is lengthened to allow time for drug elimination before redosing. Lengthening the dosing interval has been associated with a lower risk of toxicities but a higher risk of subtherapeutic drug concentrations, especially toward the end of the dosing interval\textsuperscript{49}.

\textsuperscript{48}Reuning dr. R.H.
\textsuperscript{49}Myrna Y.
2. METHODOLOGY

2.1 ARC patient surveys

Object: Patients of Hospital of Lithuanian University of Health Sciences Kaunas Clinics who have ARC.

Patient selection and amount: Patients were identified who met the following criteria:

- Hospitalized in Hospital of Lithuanian University of Health Sciences Kaunas Clinics
- Serum creatinine concentrations 50 mcmol/l or less
- Time period 2013 03 04 – 2014 08 15
- registered in the database of Kaunas Clinics data base software.

Accordingly, data from medical history books of these patients and data from the prescribed medications journals were filled in ARC patient surveys (appendix 1).

The permission of Bioethics Center was given. (appendix 2).

In total 31 patients with ARC (CrCl > 130 ml./min.) and 31 patients in comparative group (CrCl 90-130 ml./min.) were taken for analysis. All of the analysed patients had Scr values lower than 50 mcmol./l.

Methodology: To evaluate if patients suffer of ARC, a survey was made. Survey consists of general information part which include data about: department, physician’s name, date of hospitalisation, patients code, gender, weight, health status, age, blood pressure, pulse and breathing rate.

The second part of the survey includes data about patients’ used medications, dosages and dosage changes made, creatinine test results, creatinine clearance calculations and table of possible reasons of ARC. According the survey data (specifically according Cockroft-Gault equation results), patients were grouped to ARC or comparative groups, dependig on whether their CrCl was > 130 ml./min or 90-130 ml./min. To decide whether a patient belongs to the ARC group or not, the estimation of GFR rate was calculated using Cocroft-Gault formula (CrCl was the marker).

Statistical analysis:
The received data was aggregated in standard Excel summary table and evaluated statistically using appropriate software that helped to find correlations between two groups that were compared.

Microsoft Excel 2013 and SPSS 17.0 software was used for analysis. Various parameters were calculated in order to analyse the data and find out significant differences: mean values and standard deviations (X±SD) were calculated of:

- Age
- Weight
- Pulse
- GFR (according three different formulas).

Percentaged distribution was calculated and graphically presented for:

- Departments
- Diseases
- possible ARC reasons
- GFR estimations’ differences
- renally excreted drugs.

The Wilcoxon-Mann-Whitney test was applied to verify if the several data sets have enough similarities to be at all comparable (test of homogeneity)

Finally, the values of GFR estimations (using three different approaches) were analysed statistically applying the non-parametric statistical Friedmans’ test, which is generally accepted as an appropriate approach to find out significant differences between comparable data sets. A p-value <0.05 was considered to indicate a significant statistical difference between two data sets.
3. RESULTS

3.1 Patients selected for the study

For this study, patients characterized by a low creatinine level were selected (totally 62), with Scr concentrations of 50 µmol/l. or less.

31 patients with present ARC (CrCl of 130 ml/min. and higher) were selected as the investigation group A.

The same amount of patients (31) with normal CrCl (between 90-130 ml/min.) were selected as the comparative group B.

The incidence of ARC was detected by calculating approximate GFR(CrCl) according the Cockroft-Gault formula.

3.2 Patient demographic data analysis

3.2.1 Analysis by gender

Comparing the distribution of males and females in both groups there were no statistically significant differences found: in A group 54.8% and respectively 64.5% in group B were females. Comparing the male and female ARC incidence in group A there was no statistically significant differences found as well (p=0.59). Showed in the table 7 below:

<table>
<thead>
<tr>
<th>ARC group</th>
<th>Gender:</th>
<th>N</th>
<th>%</th>
<th>Chi square</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>14</td>
<td>45.2</td>
<td>0.29</td>
<td>0.590</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>17</td>
<td>54.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Comparative group

<table>
<thead>
<tr>
<th>Gender</th>
<th>N</th>
<th>%</th>
<th>Chi square</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>11</td>
<td>35.5</td>
<td>2.61</td>
<td>0.106</td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>64.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 7. Comparison of the patients by gender.

#### 3.2.2 By Age

Comparison of the groups by age showed that average age of patients in group A is 49±15.68 and in group B: 64±13.70 years,

#### Table 8. Minimum, maximum and mean of the ages of the patients in both groups.

<table>
<thead>
<tr>
<th>ARC group</th>
<th>N</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>31</td>
<td>19</td>
<td>75</td>
<td>49.03</td>
<td>15.68</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-ARC group</th>
<th>N</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>31</td>
<td>40</td>
<td>87</td>
<td>64.00</td>
<td>13.70</td>
</tr>
</tbody>
</table>

#### 3.2.3 By pulse, blood pressure and weight

Other demographic data of the patients (as showed below in the table 9) varied in both groups statistically significant only by weight as \( p<0.001 \).

The mean weight:

- group A patients: 71.70±11.80 kg
- group B patients: 62.06±7.67 kg.

Pulse rate, systolic and diastolic blood pressure did not differ significantly in both groups. Comparing both groups by pulse, \( p \) value was: \( p=0.713 \); by systolic blood pressure \( p \) value was \( p= 0.724 \) and by diastolic blood pressure: \( p= 0.176 \).
<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>Std. deviation</th>
<th>Mean Rank</th>
<th>Mann-Whitney U</th>
<th>Asymp. Sig. (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulse rate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARC group</td>
<td>31</td>
<td>85.29</td>
<td>11.66</td>
<td>32.34</td>
<td>454.5</td>
<td>0.713</td>
</tr>
<tr>
<td>Comparative group</td>
<td>31</td>
<td>86.32</td>
<td>14.05</td>
<td>30.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARC group</td>
<td>31</td>
<td>71.70</td>
<td>11.08</td>
<td>39.77</td>
<td>224</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Comparative group</td>
<td>31</td>
<td>62.06</td>
<td>7.67</td>
<td>23.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Systolic blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARC group</td>
<td>31</td>
<td>128.09</td>
<td>20.81</td>
<td>30.69</td>
<td>455.5</td>
<td>0.724</td>
</tr>
<tr>
<td>Comparative group</td>
<td>31</td>
<td>128.16</td>
<td>22.12</td>
<td>32.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diastolic blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARC group</td>
<td>31</td>
<td>79.38</td>
<td>12.05</td>
<td>34.56</td>
<td>385.5</td>
<td>0.176</td>
</tr>
<tr>
<td>Comparative group</td>
<td>31</td>
<td>75.29</td>
<td>10.49</td>
<td>28.44</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 9. Comparison of patient’s demographic data of both groups

### 3.3 Departments

In the ARC group, ARC was detected in 11 different departments of the Clinics. 29% of ARC cases were detected in ICU as expected (includes neurology and intensive therapy departments).

Rest of the ARC cases (71%) were detected in Non-ICU setting: in surgery departments 35.5% (includes surgery, spinal cord and peripheral nerves surgery and chest surgery departments) and 35.5% in therapeutic departments (endocrinology, obstetrics, gynecology, gastroenterology, hematology and allergy).

Data is shown in the Figure 3 below.
The comparative group patients were detected in 9 different departments of the Clinics.

19.4% of Non-ARC patients were detected in ICU departments.

The rest of the cases (80.6%) were found in Non-ICU setting: 36.5% of patients in surgery departments (includes head, brain, vein and cardiac surgery departments) and the rest 42% in therapeutic departments like endocrinology, gynecology, pulmonology and allergy, gastroenterology, various traumas, psychiatry and hematology.

Data is shown in the Figure 4 below.

Figure 3. Percentage of the ARC group patients (n=31) in different departments.
3.4 Factors possibly associated with ARC

For the patients of group A, several factors could be detected that are related with ARC.

Most common associated factor in ARC group was young age (defined as age below 60 years, in 70.9% of ARC group).

Other possible factors, ARC seems to be associated with:

- surgery (42 %)
- Trauma (22 %)
- diabetes (13%)
- pancreatitis (13%).

Other less frequently associated factors included stroke, burn, tetanus, nephritis, cholangitis, cystic fibrosis and vein embolism. Data is shown in the Figure 5 below.
Figure 5. Factors possibly associated with ARC in % (n=31)

Patients of comparative group who have no ARC were hospitalized because of: trauma (9.7%), pneumonia, pancreatitis, diabetes, cancer, bleeding and burns injury (6.5% each). Only 42% of them were <60 years old.

Less frequently, comparative group patients were hospitalized because of diseases like cystic fibrosis, cholangitis, peritonitis and others (3.2% each). Data is shown in the figure 6 below.

Figure 6. Reasons of comparative group’s patient hospitalization in %.
3.5 Analysis of GFR estimations

The values of GFR estimations calculated by three different formulas (Cockroft-Gault, MDRD and CKD-EPI) were compared using non-parametric Mann Whitney rank-sum test.

Mann Whitney mean ranks were calculated to compare the results as given in the table 7.

The mean GFR values of the research group were statistically different: Cockroft-Gault: 164.8±9.54 ml./min., MDRD simplified: 169.7± 9.60 ml./min./1.73 m² and by CKD-EPI 123. 3± 11.34 ml./min./1.73 m² (p<0.001).

![Figure 7. Comparison of GFR estimations according to three different formulas in ARC group.](image)
Figure 8. Comparison of GFR estimations according to three different formulas in Non-ARC group
Table 10. Comparison of GFR values calculated by three formulas.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Group</th>
<th>N</th>
<th>Mean</th>
<th>Std. deviation</th>
<th>Mean Rank</th>
<th>Mann-Whitney U</th>
<th>Asymp. Sig. (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR according MDRD simplified</td>
<td>ARC group</td>
<td>31</td>
<td>169.67</td>
<td>39.74</td>
<td>37.77</td>
<td>286</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Comparative group</td>
<td>31</td>
<td>147.61</td>
<td>35.85</td>
<td>25.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR according Cockroft-Gault</td>
<td>ARC group</td>
<td>31</td>
<td>164.81</td>
<td>34.50</td>
<td>47.00</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Comparative group</td>
<td>31</td>
<td>114.56</td>
<td>12.23</td>
<td>16.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR according CKD-EPI</td>
<td>ARC group</td>
<td>31</td>
<td>123.28</td>
<td>19.98</td>
<td>40.10</td>
<td>214</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Comparative group</td>
<td>31</td>
<td>107.42</td>
<td>9.54</td>
<td>22.90</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The proportion of ARC as assessed by MDRD was 90%, but by CKD-EPI only 29%. This means that MDRD classifies many cases as ARC patients, who are not classified as ARC patients according CKD-EPI.

It is noticeable that GFR according MDRD estimation mean values in ARC group are higher compared to Cockroft-Gault or CKD-EPI.

In the comparative group, the mean GFR estimations were also statistically different: Cockroft-Gault: 114.56±12.23 ml./min., MDRD simplified: 147.61 ± 35.85 ml./min./1.73 m² and CKD-EPI: 107.42 ± 9.54 ml./min./1.73 m² (p<0.001).

The proportion of Non-ARC as assessed by MDRD was: 25.8% and by CKD-EPI 100%. This means that CKD-EPI and Cockroft-Gault lead to exactly the same result, whereas MDRD classifies 74.2% of the patients, that have no ARC according Cockroft-Gault, as ARC patients.

Using Friedmanns’ test, GFR values calculated according three formulas were compared. The table X shows statistically significant differences between the compared values.

Calculating GFR according MDRD gave highest values of renal clearance in both groups. Comparing GFR according MDRD simplified and GFR according Cockroft-Gault with
Wilcoxon-Mann-Whitney test, statistically significant differences in ARC group were not found (p=0.493).

The table below shows the averages of the GFR estimations calculated by three formulas and compared in both groups.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Std. deviation</th>
<th>Mean rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARC group (N=31)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR according MDRD</td>
<td>169.67</td>
<td>39.74</td>
<td>2.55</td>
</tr>
<tr>
<td>simplified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR according Cocroft-Gault</td>
<td>164.81</td>
<td>34.50</td>
<td>2.45</td>
</tr>
<tr>
<td>GFR according CKD-EPI</td>
<td>123.28</td>
<td>19.98</td>
<td>1</td>
</tr>
<tr>
<td>Comparative group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N=31)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR according MDRD</td>
<td>147.61</td>
<td>35.85</td>
<td>2.89</td>
</tr>
<tr>
<td>simplified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR according Cocroft-Gault</td>
<td>114.56</td>
<td>12.23</td>
<td>1.87</td>
</tr>
<tr>
<td>GFR according CKD-EPI</td>
<td>107.42</td>
<td>9.54</td>
<td>1.24</td>
</tr>
</tbody>
</table>

Table 11. Comparison of GFR values within the ARC and non-ARC group

3.5.1 Comparison of GFR estimation values versus patients age

Patients of A and B groups were classified according the age in two groups: below 60 years old and above. The averages of GFR estimation values (according three formulas) were calculated.

It is noticeable that in ARC group mean GFR estimation values calculated by CKD-EPI equation are significantly different (p=0.001) in patients above and below 60 years old.

The values don’t differ significantly when calculated according Cocroft-Gault or MDRD formula.
In the comparative group, GFR mean estimation values differ significantly in the two age groups when calculated by CKD-EPI, but values don’t differ significantly when calculated according Cocroft-Gault (p=0.005) or MDRD (p=0.622).

<table>
<thead>
<tr>
<th>ARC group:</th>
<th>GFR according MDRD simplified</th>
<th>GFR according Cocroft-Gault</th>
<th>GFR according CKD-EPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean</td>
<td>Std. dev.</td>
<td>Mean</td>
</tr>
<tr>
<td>&lt;60 (N=23)</td>
<td>171.39</td>
<td>43.41</td>
<td>168.04</td>
</tr>
<tr>
<td>&gt;60 (N=8)</td>
<td>164.75</td>
<td>28.44</td>
<td>155.52</td>
</tr>
<tr>
<td>p=0.982</td>
<td></td>
<td>p=0.464</td>
<td>p=0.001</td>
</tr>
</tbody>
</table>

Table 12. GFR estimation means according Cockroft-Gault, MDRD and CKD-EPI versus patient’s age comparison in ARC group.

<table>
<thead>
<tr>
<th>Non-ARC group:</th>
<th>GFR according MDRD simplified</th>
<th>GFR according Cocroft-Gault</th>
<th>GFR according CKD-EPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean</td>
<td>Std. dev.</td>
<td>Mean</td>
</tr>
<tr>
<td>&lt;60 (N=13)</td>
<td>144.15</td>
<td>13.74</td>
<td>122.45</td>
</tr>
<tr>
<td>&gt;60 (N=18)</td>
<td>150.11</td>
<td>46.03</td>
<td>108.87</td>
</tr>
<tr>
<td>p=0.622</td>
<td>p=0.005</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Table 13. GFR estimation means according Cockroft-Gault, MDRD and CKD-EPI versus patient’s age comparison in comparative group.

### 3.5.2 Comparison of GFR estimation values versus patients gender

It is noticeable that in ARC group the average GFR values according MDRD differ significantly between male and female patients (184.14 vs. 157.76). Other average GFR values according Cockroft-Gault and CKD-EPI do not have significant differences. The female patients have in average higher GFR values than male patients.
Table 14. Comparison of average GFR values among male and female patients of the ARC group.

In comparative group as in ARC group the average GFR values when calculated according MDRD differ statistically significant between male and female patients. Females have in average higher GFR values as males.

Table 15. Comparison of average GFR values among male and female patients of comparative group.
3.5.3 Comparison of GFR estimation values versus serum creatinine levels

ARC group patients were grouped according serum creatinine levels into two groups: <40 µmol/l and >40 µmol/l.

22.5% (7 patients) of ARC group patients had very low serum creatinine levels (< 40 µmol/l).

It is noticeable that in patients with lower SCr levels (less than 40) mean GFR estimations are higher than in patients with Scr of (>40 ) when calculated according MDRD and Cockroft-Gault. The difference is statistically significant (p=0.003).

<table>
<thead>
<tr>
<th>Serum conc. µmol/l</th>
<th>GFR according MDRD simplified</th>
<th>GFR according Cockroft-Gault</th>
<th>GFR according CKD-EPI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Std. dev.</td>
<td>Mean</td>
</tr>
<tr>
<td>&lt;40 (N=7)</td>
<td>213.00</td>
<td>51.22</td>
<td>203.40</td>
</tr>
<tr>
<td>&gt;40 (N=24)</td>
<td>157.04</td>
<td>25.26</td>
<td>153.56</td>
</tr>
<tr>
<td></td>
<td>p=0.003</td>
<td>p=0.001</td>
<td>p=0.267</td>
</tr>
</tbody>
</table>

Table 16. Comparison of mean GFR estimations between the patients with lower SCr levels (< 40 µmol/l) and higher SCr levels (>40 µmol/l)

In comparative group 5 patients had lower serum creatinine levels (< 40 µmol/l).

It is noticeable that in patients with lower SCr levels (less than 40) mean GFR estimations are higher than in patients with Scr of (>40 ) when calculated according MDRD.

The difference is statistically significant (p=0.021).
<table>
<thead>
<tr>
<th>Serum Conc. µmol/l</th>
<th>GFR according MDRD simplified</th>
<th>GFR according Cocroft-Gault</th>
<th>GFR according CKD-EPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>Std. dev.</td>
<td>Mean</td>
<td>Std. dev.</td>
</tr>
<tr>
<td>&lt;40 (N=5)</td>
<td>192.80 63.77</td>
<td>116.94 7.90</td>
<td>110.76 10.43</td>
</tr>
<tr>
<td>&gt;40 (N=26)</td>
<td>138.92 20.12</td>
<td>114.11 12.96</td>
<td>106.78 9.45</td>
</tr>
<tr>
<td>p=0.021</td>
<td>p=0.851</td>
<td>p&lt;0.320</td>
<td></td>
</tr>
</tbody>
</table>

Table 17. Comparison of mean GFR estimations between the patients with lower SCr levels (< 40 µmol/l) and higher SCr levels (>40 µmol/l) in comparative group.

3.6 Drugs that are at risk of underdosing in case of changed renal elimination

3.6.1 Drugs taken by the patients

In both groups patients were taking in average 4 different drugs at the same time.

Two patients in ARC group were receiving 8 different drugs at the same time and two patients in the comparative group were receiving 7 different drugs at the same time.

All the drugs taken by the patients were divided into (predominantly) renally excreted drugs and (predominantly) biliary excreted drugs.

Polypharmacy (taking more than four different drugs at the same time) was noticed in 8 patients (25.8%) of ARC group and in 11 patients (35.5%) of comparative group.

87.09% of the ARC group patients were taking one or more only renally excreted drugs, whereas in comparative group it was 90.32%.

The table below compares renally and biliary drug usage in both groups.
Table 18. Comparison of renally and biliary excreted drugs in both groups (%).

Multiple classification applied.

<table>
<thead>
<tr>
<th></th>
<th>NON-ARC comparative group</th>
<th>ARC group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>No renally excreted drugs</td>
<td>4/31 12.90 %</td>
<td>3/31 9.67 %</td>
</tr>
<tr>
<td>taken</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renally and biliary excreted</td>
<td>30/31 9.77 %</td>
<td>25/31 80.64 %</td>
</tr>
<tr>
<td>drugs taken</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renally excreted drugs</td>
<td>27/31 87.09 %</td>
<td>28/31 90.32 %</td>
</tr>
<tr>
<td>taken (at least one such</td>
<td></td>
<td></td>
</tr>
<tr>
<td>drug)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.6.2 Amount of only renally excreted drugs taken by the patients

Some patients were receiving several only renally excreted drugs at the same time.

In the ARC group:

10 patients were taking 1 only renally excreted drug

12 patients were taking 2 only renally excreted drugs

3 patients were taking 3 ony renally excreted drugs

1 patient was taking 4 different only renally excreted drugs

1 patient was taking 5 different only renally excreted drugs.

The patient who received 5 only renally excreted drug therapy was female from ICU with diagnosed tetanus.

In the comparison group:

8 patients were taking 1 only renally excreted drug

13 patients were taking 2 only renally excreted drugs

4 patients were taking 3 only renally excreted drugs

2 patients were taking 4 only renally excreted drugs.
3.6.2.1 Most common only renally excreted drugs taken

In the following list is shown which only renally excreted drugs are taken most often by the patients of both groups:

In ARC group:
11 patients were taking Cefuroxim
7 patients were taking Fraxiparine
6 patients were taking Potassium Chloride
6 patients were taking Ranitidine
4 patients were taking Metoprolol
3 patients were taking Ketoprofen
2 patients were taking Diazepam
2 patients were taking Ceftazidime
2 patients were taking Furosemide
2 patients were taking Gentamycine
1 patient was taking Metformin
1 patients was taking Meropenem
1 patient was taking Gabapentine
1 patient was taking Vancomycine

In comparative group:
10 patients were taking Metoprolol
8 patients were taking Potassium Chloride
6 patients were taking Ranitidine
5 patients were taking Fraxiparine
3 patient were taking Gentamycine
3 patients were taking Diazepam
3 patients were taking Vancomycin
3 patients were taking Cefuroxim
2 patients were taking Furosemide
2 patients were taking Omeprazole
2 patients were taking Ketoprofen
2 patients were taking Pethidine
2 patients were taking Metformin
2 patients were taking Ceftazidime
1 patient was taking Metoclopramide

In a statistical view, this means that in the ARC group:

35.5% of the patients received Cefuroxim
22.5% of the patients received Fraxiparine
19.4% of the patients received KCL and Ranitidine
12.9% of the patients received Metoprolol.

Less frequently patients received Ketoprofen, Omeprazole, Diazepam, Ceftazidime, Furosemide, Gentamicine, Metformin, Meropenem, Gabapentin, Vancomycin.

In the comparative group:
32.3% of the patients received Metoprolol

25.8% of the patients received KCL

19.4% of the patients received Ranitidine

16.1% of the patients received Fraxiparine.

In comparative group, patients received less frequently Gentamycin, Diazepam, Vancomycin, Cefuroxim, Furosemide, Omeprazole, Ketoprofen, Pethidine, Metformin, Ceftazidime and Metoclopramide.

It is remarkable that Ranitidine was taken in both groups by 19.4% of the patients.

3.6.2.2 At minimal dosage given only renally excreted drugs

From those 90.2% (28/31) of ARC group patients who were receiving at least one only renally excreted drug, 24 patients were receiving at least one only renally excreted drug at minimum dosage.

77% of total ARC group patients were taking minimal doses of only renally excreted drugs

In comparative group 23 patients were receiving at least one only renally excreted drug at its minimal dosage.

74.2% of the comparative group patients were receiving only renally excreted drugs at their minimal doses.
Graph 9. Most often received drugs only renally excreted taken at minimum dosages by comparative group patients.

Figure 10. Most often received only renally excreted drugs taken at minimum dosages by ARC group patients.
CONCLUSIONS

1. In the research group and comparative groups were 31 patients selected (totally 62 patients). Based on the study results can be concluded that ARC (when glomerular filtration rate 130ml/min. and more) assessed by Cocroft-Gaul equation was not sufficiently replicated by CKD-EPI. In Non-ARC patients (when glomerular filtration rate is 90 -130 ml/min.), the absence of ARC was not sufficiently replicated by MDRD formula.

2. ARC was detected almost equally in the ICU (as expected), non-ICU surgical and non-ICU therapeutic departments.

3. The ARC-patients had several possible known risk factors, most frequently it was "young age" (below 60 years), surgery and trauma followed by less frequent risk factors as diabetes and pancreatitis. It is specifically remarkable that “young age”, which is usually meant to be associated with good health, increases the risk of ARC and therefore the risk of underdosing renally excreted drugs.

4. Most of the patients with ARC received only renally excreted drugs dosed at minimal doses. Mostly taken drugs were cefuroxim, fraxiparin, ranitidine, ketoprofen followed by less frequently taken metoprolol, gentamycine, furosemide.
DISCUSSIONS

In this study, Cockroft-Gault equation was used as reference for identifying ARC in patients with low Scr levels. Several studies were performed to compare the precise 24-hour GFR values with the mathematical approach of Cockroft-Gault. This comparison demonstrated a predominantly reliable correlation\(^{50}\). Accordingly, Cockroft-Gault GFR estimation can not be counted as the perfect approach, and it is promising to research for more appropriate formulas. On the other hand, at the moment seems to exist no better approach than Cockroft-Gault for estimating GFR values.

According Levey\(^{51}\), the CKD-EPI equation is most accurate in determining approximate GFR. In contrast, according to the present study CKD-EPI failed to detect ARC cases compared to Cockroft-Gault.

Camargo\(^{52}\) et al. concluded in their study that CKD-EPI underestimated GFR in patients with diabetes. In the present study, 13% of the ARC patients were diabetic, which can partially explain the failure of CKD-EPI in detecting ARC cases.

Results of this study suggests that ARC patients are not only to be found in ICU, but can also be detected in other therapeutic departments. In the present study, detection of ARC cases in ICU and non-ICU departments was almost equal.

This study corresponds with the opinion that „ARC phenomenon is a significant event in patients in any hospital department“.\(^{53}\).

\(^{50}\) Poggio, 242-252
\(^{51}\) Levey, 622
\(^{52}\) Camargo, 90-95
\(^{53}\) Minkute et al, 462-467
1. For this study, patients with low SCr levels were choosen, but only few ARC case studies conclude that ARC can also be detected in patients with normal serum creatinine levels. Future studies of ARC should also include patients with normal and low Scr levels in order to better evaluate the incidences of ARC.

2. As this study shows, ARC can be found not only in ICU settings, but also in Non-ICU. Physicians and other hospital staff of Non-ICU departments should keep in mind that various factors like traumas, surgeries, diabetes and pancreatitis are as well risk factors of ARC and such patients are predisposed to subtherapeutic drug levels of only renally excreted drugs.

3. As one study concludes, daily measurement of GFR and therapeutic drug monitoring allows the drug therapy to achieve the therapeutic range. To achieve best possible medication, it is necessary to increase the awareness of drug dose monitoring and adjustment in all cases of expected abnormalities of kidney function.

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55 Tröger, YYY
REFERENCES


6. Cockcroft D. W., Gault M. H. Prediction of creatinine clearance from serum creatinine. 1976. Departments of Medicine, Queen Mary Veterans’ Hospital, Montreal, Quebec, and Memorial University; St. John’s, Newfoundland, Canada.


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18. Levey A. S., Stevens L. A., MD, MS, FRCP(C), Schmid C.H., PhD, Zhang Y.L., MS, Castro A.F., Feldman H., MD, MSCE, Kusek J.W., Eggers P., PhD, Van Lente F.,


41.
APPENDIXES

1 Appendix. ARC patient survey

Augmented renal clearance (ARC) survey No. ______

________________________
Date of the first observation

I. General information

Clinic, department

Doctor`s name

Patient`s case history No.

Patient`s code

Date of hospitalization

Disease code

Gender (M/F)

Age

Height

Weight

General health status

Blood pressure

Pulse rate

Breathing rate

2. Diagnosis (main condition, complications)
II. Data about kidney damage

<table>
<thead>
<tr>
<th>Initial creatinine conc. (Cre)</th>
<th>Creatinine clearance was calculated: (Cockcroft Gault: ( \text{CrCl} = (\text{A} \times (140 - \text{age}) \times \text{weight})/\text{Cre} ))</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td>MDRD</td>
<td>CKD-EPI</td>
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</tbody>
</table>

1. Currently used medication (data is written during the first day of investigation, changes made – in case dosing changed, since when and how long)

<table>
<thead>
<tr>
<th>Name, dosing, changes made and date</th>
<th>Name, dosing, changes made and date</th>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>13.</td>
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<td>2.</td>
<td>14.</td>
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<tr>
<td>3.</td>
<td>15.</td>
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<td>4.</td>
<td>16.</td>
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<td>5.</td>
<td>17.</td>
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<td>6.</td>
<td>18.</td>
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<td>7.</td>
<td>19.</td>
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</table>
2. Laboratory test results *(In case of ARC data is registered starting from the beginning of ARC!)*

<table>
<thead>
<tr>
<th>Date</th>
<th>Result and comment</th>
<th>Date</th>
<th>Result and comment</th>
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</tbody>
</table>

3. ARC influence on the treatment

<table>
<thead>
<tr>
<th>Date</th>
<th>Influence on the treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

4. Laboratory data to evaluate the impact of ARC

<table>
<thead>
<tr>
<th>Laboratory tests/data, efficiency</th>
<th>Laboratory tests/data, safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td>Result and comment</td>
</tr>
<tr>
<td>------</td>
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</tbody>
</table>

5. Possible reasons for ARC

- Younger age (<60 years)
- Pregnancy
- Sepsis
- Trauma
- Surgery or neurosurgery
- Neutropenia
- Burns injury
- Cystic fibrosis
- Other

6. Patient belongs to group:

<table>
<thead>
<tr>
<th>ARC (CrCl &gt;130 ml/min.)</th>
<th>Control group (CrCl 90-130 ml/min.)</th>
<th>Not included to investigation (CrCl &lt; 90 ml/min.)</th>
</tr>
</thead>
</table>