Renal Disease and Transplantation Forum
2023, vol. 16, no. 1, 8–13

ISSN 2720–2771
e-ISSN: 2720-4189
DOI: 10.5603/RDTF.2023.0006

VIA MEDICA

Wojciech Wołyniec

Nephrology Department, Szpitale Pomorskie, Gdynia, Poland
Department of Occupational, Metabolic, and Internal Medicine, Medical University of Gdańsk, Poland

Bloodletting. Dead end in medicine or an endless inspiration for modern nephrology? Part 1

ABSTRACT

Nowadays bloodletting is used as a treatment for polycythemia and hemochromatosis. However, for centuries it was used to treat numerous other diseases, mostly without any justification. The idea of bloodletting was to remove the excess of one of the *humors* — blood. Indeed, in patients with hypertensive crisis or acute heart failure, the removal of fluid excess could lead to an improvement. Bloodletting has now been replaced by diuretics and ultrafiltration, which are essential parts of extracorporeal renal replacement therapy. This article provides an overview of the history and physiological basis of bloodletting.

Renal Disease and Transplantation Forum 2023, vol. 16, no. 1, 8–13

Key words: bloodletting, arterio-venous fistula, dropsy, diuretics, renal replacement therapy

In this article, I provide a couple of excerpts from the literature. Trying not to ruin the fun of guessing the authors, I provided their names at the very end.

INTRODUCTION

Bloodletting is usually treated as bizarre, ineffective, and harmful therapy known from the history of medicine [1–5]. Although it is still used to treat polycythemia and hemochromatosis, it is considered a sham in other indications [2, 5, 6]. Similar views are held to related therapies in traditional medicine such as leech therapy or 'bloody' cupping [7, 8].

As an educated and experienced 'conventional' physician of Western medicine, I would like to put my prejudice aside and reflect on the real value and risk of bloodletting.

HISTORICAL OUTLINE — THE BEGINNING

The European history of bloodletting dates back at least 2500 years ago [6, 9]. It was described in the work of Hippocrates (ca. 460 BCE–370 BCE), Aulus Cornelius Celsus (53 BCE–7 BCE), and Galen (ca. 129 CE–ca. 200 CE) [3, 4].

However, the real origins of this method are lost in the mists of time [4]. We can find scenes of bloodletting in Homer's *Iliad* and Herodotus's *Histories* [3, 4, 9]. We know that it was practiced by ancient peoples of Mesopotamia and Egypt more than 1000 years before the common era [2, 4, 5, 9]. Bloodletting was not uncommon in Jewish, Arabic, Chinese, or Indian medicine [4, 9] and was also practiced by the Mayans [2, 10], African tribes, and indigenous people of Tasmania and Fiji [9].

Given the widespread use of bloodletting, it seems that there were no cultural or time limits in its application. Perhaps one author's observation that bloodletting is '*as old as humanity itself*' is true [6].

In ancient times, bloodletting was practiced by the medics who were well-educated; later by clerics in Europe until 1163 AD when, during the Council of Tours, Pope Alexander III proclaimed a decree prohibiting the clergy from such practices [11]. Since then, bloodletting and other minor surgical procedures were mainly practiced by barbers. It was also when: '*the morals of the workers fell to a low ebb comparable only to their competence*' [4].

Address for correspondence:
Wojciech Wołyniec,
Oddział Nefrologiczny,
Szpitale Pomorskie w Gdyni,
ul Powstania Styczniowego 1,
81–519 Gdynia,
tel.: +48 58 7260490
e-mail: wolyniecwojtek@gmail.com

A testimony of practicing barbers can be found in the 17th-century novel:

"(…) in that region there were two villages, one so small it had neither an apothecary's shop nor a barber, and another one nearby that did. So, the barber from the larger village served the smaller one; and in the latter village there was a sick person who needed to be bled and another who needed a shave, and for that reason the barber had a basin made of brass with him" [12].

TRADITION AND INSPIRATION

In the history of humanity, bloodletting has always been the domain of educated classes initiated into this difficult art, which is, of course, burdened with the risk of numerous complications. Those procedures were associated with risk of injury to the nerves or arteries, so some anatomical knowledge was necessary — that of an educated physician or an agile barber [9]. One of the described sequelae was an arteriovenous fistula [13]. Arteriovenous fistulas are considered a significant pathology because they interfere with physiological blood circulation. However, today we know that it is possible to live for many years with arteriovenous fistulas; moreover, chronic hemodialysis patients can live precisely because they have such fistulas.

It is probably unlikely that Cimino and Brescia were inspired by this complication of bloodletting when planning to create the first fistula for dialysis, but they were probably aware that the accidental combination of an arterial and venous vessel does not necessarily have an adverse effect on the patient. Today, we know even more; in several articles published in recent years, it has been shown that creation of an arteriovenous fistula can slow progression of renal failure [14, 15]. This is probably due to improved renal blood supply as a result of a decrease in peripheral resistance. In some patients, such a fistula has a positive effect on the circulatory system. On the other hand, harmful effects of arteriovenous fistulas on the health of chronic dialysis patients are an important factor influencing their life expectancy [16].

Over the centuries and across various cultures, bloodletting took different forms. There were many tools for cutting the skin, and blood was collected in various vessels, such as the copper basin mentioned above. For this reason, in addition to descriptions of bloodletting in the literature, there are also many artifacts used for bloodletting.

In Western medicine, we also have evidence of bloodletting. One of the most prestigious and oldest medical journals dating back to 1823 is *the Lancet,* whose name comes from a tool used for bloodletting (from the Latin *lancet*, little lance) [1]. Another highly respected and prestigious journal, the *New England Journal of Medicine* was first published in 1812, and the very first published article was titled 'Remarks on angina pectoris' and included a discussion of the impact of bloodletting on the course of the disease. The patient described in this article did not survive [17].

BLOODLETTING AND THE HUMORAL THEORY

Considering the role of bloodletting in the history of humanity, a few questions should be asked. If this method has been used for hundreds of years, then it seems reasonable that there must be some evidence that this treatment was effective at least in some patients? If so, why? What was the purpose of bloodletting — removing excess blood or any harmful substances contained in it? According to Hippocrates, the rationale for bloodletting was removing excess blood, one of the four body fluids, or 'humors' [9]. Blood, if it was in excess, was supposed to be harmful. In the Talmud, it was written even more radically: *'I, blood, am the cause of all sickness'* [18]. As a reminder, the other three body fluids (humors) that were thought to cause diseases included yellow bile, black bile, and phlegm [19].

Explaining the causes of diseases by an excess of one of the four fluids is insufficient in the 21st century although in some ways this concept is still alive. The humoral theory, which survived for more than 2000 years in Western medicine [2, 9], also had an impact on Eastern medicine; in turn, Eastern medicine inspires many European physicians even today. We can read about the humoral theory today in the official WHO publications on the so-called 'Unani medicine' [20].

IS THE LOSS OF A SMALL AMOUNT OF BLOOD A PATHOLOGY OR PHYSIOLOGY?

Blood loss is commonly thought of as a pathology and so bloodletting, in principle, should be considered harmful. However, in the history of humanity, the loss of a small amount of blood was the norm. Women lose blood during menstrual cycles and childbirth. For centuries, men bled to death as a result of minor injuries due to fights, hunting, or physi-

▶▶ Considering the popularity of bloodletting, it seems that there were no cultural or temporal limits to its application. ◀◀

cal work. Exposure to blood-sucking parasites was also common.

Life close to nature, deprived of modern comfort, was a life in which blood was often lost. The common presence of blood in the history of humanity is illustrated by the following excerpt:

There is a particular kind of science that exists on these sorts of estates — the science of coaxing out bloodstains. For centuries it has been taught to future wives and mothers. If a university for women ever came about, it would be the most important subject. Childbirth, menstruation, war, fights, forays, pogroms, raids — all of it sheds blood, ever at the ready just beneath the skin. What to do with that internal substance that has the gall to make its way out, what kind of lye to wash it out, what vinegar to rinse it with? Perhaps try dampening a rag with a couple of tears and then rubbing carefully. Or soak in saliva. It befalls sheets and bedclothes, underwear, petticoats, shirts, aprons, bonnets and kerchiefs, lace cuffs and frills, corsets, and sukmanas. Carpets, floorboards, bandages, and uniforms [21].

Humans have evolved over millennia while being exposed to frequent blood loss. So maybe this lack of blood loss is unfavorable? After all, honorary blood donors are healthy people, and multiple blood donations do not cause deterioration of their health [6], while many possible complications of blood donation are fortunately rare [22]. Interestingly, the typical volume of blood collected at blood donation centers, 450 mL [23], is about the same volume of blood lost during single bloodletting (in the English literature it was usually one pint) [4]. We also consider professional athletes to be very healthy, even though they can lose blood as a result of injuries or endovascular hemolysis [24].

Even if the loss of a small amount of blood does not bring health benefits, it was and still is so commonplace that it is hard to say that it always leads to significant pathologies. Blood was common in everyday life and was always treated in a special way — after all, it was the only substance of its kind; '*Blut ist ein Ganz besondrer Saft*/Blood is a very special juice', as Mephistopheles described it in Goethe's immortal work [25].

Even if the loss of a small amount of blood does not bring health benefits, it was and still is so common that it is hard to say that it always leads to significant pathologies.

WHAT IS THE PHYSIOLOGICAL BASIS OF BLOODLETTING?

A method that was used for centuries could not be completely ineffective and certainly not always harmful. Also, there must have been cases of spectacular healing, which prompted physicians to repeat this procedure in other patients. Of course, the physicians were aware of the limitations and dangers of this method. As described in *The dictionary of general medicine, surgery and the art of raising cattle, or the village doctor*: *'The art of medicine does not have a treatment more effective than bloodletting for many diseases. But this type of treatment, which can be so salutary in the hand of a prudent physician, [...] is a deadly sword when used indiscernibly and only by a blind habit'* (translated from original polish version) [13].

The idea of removing excess blood or blood-containing abnormal or excessive substances can be considered the theoretical basis of bloodletting. The primary contraindication would be the lack or deficiency of one of blood ingredients (therefore, bloodletting was not used in young children and elderly people who have less blood) [13]. What are the blood ingredients and what can be removed by bloodletting?

Blood accounts for about 7% of the human body and has a volume of about 5 to 6 liters. On average, 44% of blood is red blood cells. The plasma consists of 90% of water and 8% of protein. There are numerous substances in the plasma such as glucose, amino acids, fatty acids, electrolytes, and many others, including toxins — like endogenous uremic toxins or exogenous toxins consumed with food [26]. Bloodletting can be used to remove excess water, red blood cells, proteins, and other substances found in plasma.

REMOVING EXCESS WATER

The main component of blood is water. As it is known, the correct amount of water in the body is necessary for good health, and its excess can accompany many diseases. For millennia, one of the most severe diseases was dropsy. Until William Withering introduced the use of digitalis in 1785 [27], and later when in the 20th century diuretic agents were discovered, dropsy was incurable.

No wonder that healing of dropsy was one of the greatest of Jesus's miracles, in addition to healing of other hopeless cases such as blindness or claudication. In addition, Jesus performed this miracle on the Sabbath, which proves that without immediate help the patient would most likely not have survived:

One Sabbath, when Jesus went to eat in the house of a prominent Pharisee, he was being carefully watched. There in front of him was

a man suffering from abnormal swelling of his body. Jesus asked the Pharisees and experts in the law, "Is it lawful to heal on the Sabbath or not?" But they remained silent. So taking hold of the man, he healed him and sent him on his way. Then he asked them, "If one of you has a child or an ox that falls into a well on the Sabbath day, will you not immediately pull it out?" And they had nothing to say [28]. Unfortunately, as far as dropsy is concerned, bloodletting could help only very little. The loss of several hundred milliliters of blood could not change the fate of patients with severe fluid overload and resulting heart failure. However, it could bring them temporary relief in terms of shortness of breath, which was probably thought to be a confirmation of the effectiveness of this method and prompted further bloodletting sessions, until inevitable death. In the case of patients with cirrhosis or nephrotic syndrome, however, such treatment could only cause harm.

Definitely more spectacular effects must have been seen in patients with pulmonary edema. Bloodletting was used intuitively or deliberately and undoubtedly saved many human lives. After learning the physiology and pathology of circulation, it was used many years after World War II as recognized therapy. In the Polish literature, there is a beautiful, although tragic, description of treatment for pulmonary edema:

I was breathing hard, grasping for air with my mouth wide open, I was getting some nasty whistles out of my throat. I reached the door of the sanatorium and completely exhausted sat on the steps. Returning from the walk, the patients dragged me to the stairs and took me to the nurses' office. Someone ran for the doctor. I was lying down and choking. I couldn't breathe. The doctor, who came in a hurry, thought for a while and decided to put a thick needle in my straightened arm. A narrow, dark stream of blood flowed down into a glass. I suffocated. Between wheezing breaths I shouted — "Mom! — and — I don't want to die!" When the glass was filled with blood, I felt relief. My breath was coming back [29]. Nowadays, thanks to diuretics, bloodletting for pulmonary edema is not used anymore. However, in the case of a patient with anuria, if there is no possibility of immediate dialysis, and the patient is dying of choking, this can still be the only solution [6], except for a sitting position and applying a compression band. Medicine is changing rapidly; treatment of acute heart failure with compression bands today sounds definitely archaic, but, in the 1970s, it was still the subject of serious research [30]. Also, there was a discussion about the superiority of bloodletting over a tourniquet on the pages of the respectable *New England Journal of Medicine* [31].

The volume of circulating blood determines arterial pressure. At a time when antihypertensives had not been discovered, blood loss could effectively lower blood pressure and help in hypertension emergencies such as in cases of neurological complications. Certainly, it must have improved headaches in patients with hypertension. This is exemplified by another excerpt:

The first case was a gentleman of this city, *about forty years of age. When he came under my care he was engaged in commercial purchases, in which he had overtaken his brain; was a man of short statue, short neck, and very tribal. Was attacked during the extreme heat of summer, with active determination of blood to the brain; there was profound coma with extreme dispersion to the vessels of the face, which was turgid with blood; there were also violent conversions. The pulse was full and bounding. I opened a vein in the arm, and bled him copiously. He immediately regained his consciousness, the convulsions ceased, and the ceremonial functions were restored to their normal condition* [32].

▸▸ Bloodletting used intuitively or thoughtfully undoubtedly saved many human lives ◂◂

INSPIRATIONS

For hundreds of years physicians and barbers attended to patients with hypervolemia. They were undoubtedly aware that the cause of the disease was an excess of water. It is reflected by the Polish term *puchlina wodna* (literally 'water swelling'). The English word *dropsy* also relates to water. The word *ydropsy* (*idropsie*) in Middle English was derived from Old French *idropsie*, which in turn came from the Greek word *hydrōps* related to *hydōr* meaning water [33].

For centuries, it was technically impossible to remove water from blood while leaving out the other components. Currently, water can be removed from the body using one of the extracorporeal methods or with diuretics.

During slow continuous ultrafiltration (SCUF), blood flows through a semi-permeable membrane, which filters deproteinized plasma, and the other blood components are returned to the body. In SCUF, ultrafiltration is not accompanied by diffusion, and thus it is not a type of renal replacement therapy but rather a dehydration method. SCUF is a method of choice in patients with heart failure with

preserved renal function. However, renal function is usually compromised in patients with heart failure leading to cardio-renal syndrome, and in such cases, the method of choice is continuous veno-venous hemofiltration (CVVH) or intermittent hemodialysis (IHD). In CVVH, the total ultrafiltration volume is much higher compared with SCUF, and the use of replacement fluid is necessary. Therefore, it allows not only for removal of excess water but also uremic toxins [34, 35].

SCUF resembles bloodletting for hypervolemia or hypertensive crisis and would certainly be favored by barbers. For more subtle physicians, another way of removing water would be more suitable such as diuretic drugs.

The history of putative diuretic drugs is as long as the history of medicine itself; however, the history of effective strong-acting diuretics is much shorter. The first 'functional' diuretic was digitalis (foxgloves). The leaves of this beautiful plant, when taken in small amounts, cause increased diuresis in patients with dropsy due to heart failure. The increase in diuresis was a result of the plant's positive inotropic effect on the heart muscle. Unfortunately, digitalis is toxic in excessive amounts, and to date, it is a perfect example of a drug with a narrow therapeutic index, which is reflected by Parcelsus' words 'Sola dosis facit venemum' (lit. only the dose makes a poison).

Classic diuretics, i.e. carbonic anhydrase inhibitors, thiazides, loop diuretics, and potassium-sparing agents are substances that have achieved incredible success and popularity in medicine. Undoubtedly, they are one of the most commonly used drugs. Even a brief discussion of those drugs would go beyond the scope of this article. However, three new substances have joined this group of miracle drugs, and they are worth mentioning.

Vaptans, gliflozins, and finerenone are new drugs in nephrology, and they all belong to the family of diuretics.

The vasopressin V2 receptor antagonists are called vaptans. Theoretically, they are ideal diuretics because they are the only ones that do not have a natriuretic effect but only an aquaretic one; in other words, they increase excretion of water but not sodium. Interestingly, the greatest hopes with those drugs are associated with their pleiotropic effect due to lowered intracellular cyclic adenosine monophosphate (cAMP) concentration in renal tubular cells [36]. One of the drugs in this group, tolvaptan, is the only drug to slow progression of adult polycystic kidney disease [37].

The second new group of drugs acting on the renal tubules is gliflozins, i.e. sodium-glucose co-transporter 2 (SGLT2) inhibitors. By blocking SGLT2, those drugs also reduce the reabsorption of sodium in the proximal tubule. Inhibition of sodium reabsorption in the proximal tubule, by affecting tubulo-glomerular feedback, is responsible for pleiotropic properties of flosins, primarily their nephroprotective effect [38].

The third drug raising hopes among nephrologists is finerenone, which is classified as a potassium-sparing diuretic or aldosterone antagonist. Vaptans, gliflozins, and finerenone are new drugs in nephrology, and each of them belongs to the family of diuretics.

Diuretic therapy is a basic component of treatment for cardiovascular and renal diseases. If we cannot imagine ourselves being doctors without diuretics and extracorporeal renal replacement therapy, we can understand why our predecessors did not imagine medicine without bloodletting. Or we have no imagination.

CONFLICT OF INTEREST

None to declared.

References

1. Bynum B, Bynum H. Lancet. Lancet. 2015; 386(9997): 945, doi: 10.1016/S0140-6736(15)00108-7, indexed in Pubmed: 26369459.
2. Cook LS. Therapeutic phlebotomy: a review of diagnoses and treatment considerations. J Infus Nurs. 2010; 33(2): 81–88, doi: 10.1097/NAN.0b013e3181d00010, indexed in Pubmed: 20228645.
3. Hines LE. Benjamin Rush, venesectionist. Q Bull Northwest Univ Med Sch. 1947; 21(1): 61–64, indexed in Pubmed: 20295103.
4. Holman DV. Venesection, before Harvey and after. Bull N Y Acad Med. 1955; 31(9): 661–670, indexed in Pubmed: 13250305.
5. Jhang JS, Schwartz J. Phlebotomy or bloodletting: from tradition to evidence-based medicine. Transfusion. 2012; 52(3): 460–462, doi: 10.1111/j.1537-2995.2012.03548.x, indexed in Pubmed: 22404509.
6. van Tellingen C. Bleeding-edge technology in cardiology - or the mixed blessings of phlebotomy throughout the ages. Neth Heart J. 2010; 18(4): 218–222, doi: 10.1007/BF03091765, indexed in Pubmed: 20428422.
7. Mory RN, Mindell D, Bloom DA. The leech and the physician: biology, etymology, and medical practice with Hirudinea medicinalis. World J Surg. 2000; 24(7): 878–883, doi: 10.1007/s002680010141, indexed in Pubmed: 10833259.
8. Aboushanab TS, AlSanad S. Cupping Therapy: An Overview from a Modern Medicine Perspective. J Acupunct Meridian Stud. 2018; 11(3): 83–87, doi: 10.1016/j.jams.2018.02.001, indexed in Pubmed: 29436369.

9. Parapia LA. History of bloodletting by phlebotomy. Br J Haematol. 2008; 143(4): 490–495, doi: 10.1111/j.1365-2141.2008.07361.x, indexed in Pubmed: 18783398.
10. Munson J, Amati V, Collard M, et al. Classic Maya bloodletting and the cultural evolution of religious rituals: quantifying patterns of variation in hieroglyphic texts. PLoS One. 2014; 9(9): e107982, doi: 10.1371/journal.pone.0107982, indexed in Pubmed: 25254359.
11. Jones FA. The Norwich schools of surgery. The evolution of surgery in an English city. Ann R Coll Surg Engl. 1976; 58(3): 203–221, indexed in Pubmed: 773251.
12. de Cervantes M. Don Quixote. Chapter XXI. http://cervantes.tamu.edu/V2/CPI/TEI/TEI/1605/1605/1605/chapter21.html.
13. Wieniawska A. Metoda humoralna, metoda sympatyczna, wiara w magię i panaceum. . In: Karpiński A. ed. Wśród córek Eskulapa: szkice z dziejów medycyny i higieny w Rzeczypospolitej XVI-XVIII wieku. Instytut historyczny UW : 265–277.
14. Bénard V, Pichette M, Lafrance JP, et al. Impact of Arteriovenous fistula creation on estimated glomerular filtration rate decline in Predialysis patients. BMC Nephrol. 2019; 20(1): 420, doi: 10.1186/s12882-019-1607-4, indexed in Pubmed: 31760936.
15. Golper TA, Hartle PM, Bian A. Arteriovenous fistula creation may slow estimated glomerular filtration rate trajectory. Nephrol Dial Transplant. 2015; 30(12): 2014–2018, doi: 10.1093/ndt/gfv082, indexed in Pubmed: 25888388.
16. Amerling R, Ronco C, Kuhlman M, et al. Arteriovenous fistula toxicity. Blood Purif. 2011; 31(1-3): 113–120, doi: 10.1159/000322695, indexed in Pubmed: 21228578.
17. Greene JA, Jones DS, Podolsky SH. Therapeutic evolution and the challenge of rational medicine. N Engl J Med. 2012; 367(12): 1077–1082, doi: 10.1056/NEJMp1113570, indexed in Pubmed: 22992071.
18. Rosner F. Bloodletting in talmudic times. Bull N Y Acad Med. 1986; 62(9): 935–946, indexed in Pubmed: 3542099.
19. Kambic HE, Nosé Y. Historical perspective on plasmapheresis. Ther Apher. 1997; 1(1): 83–108, doi: 10.1111/j.1744-9987.1997.tb00020.x, indexed in Pubmed: 10225788.
20. World Health Organization (2010). Benchmarks for training in traditional / complementary and alternative medicine: Benchmarks for training in Unani medicine. World Health Organization. https://apps.who.int/iris/handle/10665/4435.
21. Tokarczuk O. The Books of Jacob (translated by Jennifer Croft). https://www.goodreads.com/book/show/58276619-the-books-of-jacob.
22. Rosiek A, Pogłód R. Niepożądane reakcje u krwiodawców oddających krew i jej składniki metodą manualną i automatyczną. Journal of Transfusion Medicine. 2014; 7(3): 73–83.
23. https://www.gov.pl/web/nck/czesto-zadawane-pytania.
24. Lippi G, Sanchis-Gomar F. Epidemiological, biological and clinical update on exercise-induced hemolysis. Ann Transl Med. 2019; 7(12): 270, doi: 10.21037/atm.2019.05.41, indexed in Pubmed: 31355237.
25. Schurek HJ, Neumann KH, Schweda F, Czogalla JA. Laboratory manual of kidney perfusion techniques. University of Münster, Münster (Germany) 2017.
26. https://pl.wikipedia.org/wiki/Krew.
27. Whayne TF. Clinical Use of Digitalis: A State of the Art Review. Am J Cardiovasc Drugs. 2018; 18(6): 427–440, doi: 10.1007/s40256-018-0292-1, indexed in Pubmed: 30066080.
28. Bible, Luke 14:1-6. https://www.biblegateway.com/passage/?search=Luke%2014%3A1-6&version=NIV.
29. Poświatowska H. Opowieść dla przyjaciela. In: Dzieła Tom 3. Wydawnictwo Literackie, Kraków : 46.
30. Habak PA, Mark AL, Kioschos JM, et al. Effectiveness of congesting cuffs ("rotating tourniquets") in patients with left heart failure. Circulation. 1974; 50(2): 366–371, doi: 10.1161/01.cir.50.2.366, indexed in Pubmed: 4846643.
31. Posner MD. Letter: Cardiac failure: tourniquets vs. phlebotomy. N Engl J Med. 1974; 290(26): 1485–1486, doi: 10.1056/NEJM197406272902612, indexed in Pubmed: 4831765.
32. Post AC. Curative effects of blood-letting (1867). Bull N Y Acad Med. 1968; 44(9): 1187–1189, indexed in Pubmed: 4875590.
33. https://www.etymonline.com/word/dropsy.
34. Kamath SA. The role of ultrafiltration in patients with decompensated heart failure. Int J Nephrol. 2010; 2011: 190230, doi: 10.4061/2011/190230, indexed in Pubmed: 21151532.
35. Ricci Z, Romagnoli S, Ronco C. Renal Replacement Therapy. F1000Res. 2016; 5, doi: 10.12688/f1000research.6935.1, indexed in Pubmed: 26918174.
36. Di Mise A, Wang X, Ye H, et al. Pre-clinical evaluation of dual targeting of the GPCRs CaSR and V2R as therapeutic strategy for autosomal dominant polycystic kidney disease. FASEB J. 2021; 35(10): e21874, doi: 10.1096/fj.202100774R, indexed in Pubmed: 34486176.
37. Torres VE, Chapman AB, Devuyst O, et al. TEMPO 3:4 Trial Investigators. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med. 2012; 367(25): 2407–2418, doi: 10.1056/NEJMoa1205511, indexed in Pubmed: 23121377.
38. Vasquez-Rios G, Nadkarni GN. SGLT2 Inhibitors: Emerging Roles in the Protection Against Cardiovascular and Kidney Disease Among Diabetic Patients. Int J Nephrol Renovasc Dis. 2020; 13: 281–296, doi: 10.2147/IJNRD.S268811, indexed in Pubmed: 33149657.