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Medicine

CHRONIC KIDNEY DISEASE IN CONGENITAL HEART DISEASE PATIENTS

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ABSTRACT:
CONGENITAL HEART DISEASE PREDISPOSES TO DEVELOPMENT OF CHRONIC KIDNEY DISEASE, BECAUSE OF THE PATHOPHYSIOLOGICAL CHANGES THAT OCCURS DUE TO AN ABNORMAL STRUCTURAL AND FUNCTIONAL HEART, SUCH AS CHRONIC HYPOXIA AND ANOMALIES IN THE RENAL BLOOD FLOW. ALSO, RENAL FUNCTION IS AFFECTED NOT ONLY BECAUSE OF THE PATHOPHYSIOLOGICAL CHANGES, BUT ALSO BY THE SURGICAL CORRECTION OF THE HEART ANOMALY. CURRENT STUDIES NOTICED THAT CRONIC KIDNEY DISEASE HAS A HIGHER INCIDENCE IN PATIENTS WITH CONGENITAL HEART DISEASE. DATA FROM LITERATURE SUGGEST THAT 30 TO 50% OF PATIENTS WITH CONGENITAL HEART DISEASE WILL PRESENT RENAL DYSFUNCTION.

KEY WORDS: CONGENITAL HEART DISEASE, CHRONIC KIDNEY DISEASE, CARDIAC SURGERY

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INTRODUCTION

Congenital heart disease is a heart anomaly present at birth that affects the heart walls, the heart valves or the blood vessels.

Congenital heart diseases are classified in cyanotic and noncyanotic. Cyanotic congenital heart diseases are represented by tetralogy of Fallot and transposition of the great arteries. Noncyanotic congenital heart disease are represented by left-to-right shunts (such as ventricular septal defect, persistent ductus arteriosus and atrial septal defect) and outflow obstruction (such as pulmonary stenosis, aortic stenosis and coarctation of aorta)[7].

The incidence of congenital heart disease varies from 4/1000 births to 50/1000 births. The prevalence of the mild form of congenital heart disease is increasing. The most common type of congenital heart disease is ventricular septal defect. 25% of babies with congenital heart disease have a severe form[8].

Patients with congenital heart disease have multiple risk factors for developing chronic kidney disease (CKD), because in structurally and functionally abnormal heart are pathophysiological changes. These changes include chronic hypoxia, changes in the renal blood flow and hemodynamics and, also, changes in neurohormonal system[9].

MAIN TEXT

PATHOPHYSIOLOGY

Chronic hypoxia that occurs in cyanotic congenital heart disease stimulates erytropoetin, resulting erythrocytosis, with increased blood viscosity. Studies on this issue observed that hyperviscosity affects renal hemodynamics[10]. Also, the same studies established that hyperviscosity is associated with changes at glomerular level[11].

Other studies conducted by Paswell et al., have found that congenital heart diseases are associated with decreased glomerular filtration rate (GFR), the glomerular function being improved after the surgical correction of the heart[12]. It was observed that adults with tetralogy of Fallot, which was surgically corrected in childhood, with history of decreased GFR, at the assesment at 20 years, had an increased filtration fraction[13]. Burlet et al. observed that in

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[7] Baumgartner H., Bonhoeffer P., De Groot N et al. *ESC Guidelines for the management of grown-up congenital heart disease*. European Heart Journal. 2010;31:2915-2957

[8] Marelli AJ, Mackie AS, Ionescu-Ittu R et al. *Congenital heart disease in the general population: changing prevalence and age distribution*. Circulation. 2007;1152:163–72

[9] Billett J, Cowie MR, Gatzoulis MA et al. *Comorbidity, healthcare utilisation and process of care measures in patients with congenital heart disease in the UK: cross-sectional, population-based study with case-control analysis*. Heart. 2008;949:1194–9.

[10] Cordina RL, Celermajer DS. *Chronic cyanosis and vascular function: implications for patients with cyanotic congenital heart disease*. Cardiol Young. 2010;203:242–53.

[11] DeFilippis AP, Law K, Curtin S, Eckman JR. *Blood is thicker than water: the management of hyperviscosity in adults with cyanotic heart disease*. Cardiol Rev. 2007;151:31–4.

[12] Perloff JK, Latta H, Barsotti P. *Pathogenesis of the glomerular abnormality in cyanotic congenital heart disease*. Am J Cardiol. 2000;8611:1198–204.

[13] Morgan C, Mohammed Al-Aklabi, Gonzalo Garcia Guerra. *Chronic kidney disease in congenital heart disease patients: a narrative review of evidence*. Canadian Journal of Kidney Health and Disease. 2015; 2:27

congenital heart diseases with cyanosis, the renal blood flow is reduced, resulting in hyperfiltration due to hyperviscosity and glomerular high pressure[14].

On the other hand, high glomerular pressure with an increased filtration fraction results in nephrological changes and glomerulosclerosis[15].

In a study conducted by Spear et al, in adults with congenital heart diseases and cyanosis, was described giant glomeruli, because of the dilated arterioles, increased glomerular capillar diameter, due to hyperviscosity[16].

Also, hypoxia induces renal changes, with interstitial fibrosis and abnormal renal structure[17].

Neurohormonal disorders, such as increased levels of atrial natriuretic peptide, aldosterone and renin, are also present in congenital heart disease with kidney dysfunction.

Numerous studies noticed the relationship between congenital heart diseases and CKD development[18]. In a study conducted by Aperia, decreased renal function was observed in 5 out of 10 patients diagnosed with tetralogy of Fallot[19]. Also, Dittrich et al observed that cyanotic heart disease is associated with decreased GFR[20].

Patients with congenital heart disease present proteinuria, another marker of renal dysfunction in these cases. Flanagan et al. observed that proteinuria is more frequent in patients with cyanotic heart disease[21].

Cyanotic heart disease is associated with glomerular injury. Congenital heart diseases are associated with glomerular changes and abnormalities of the renal tubular function. In a study

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[14] Ohuchi H, Takasugi H, Ohashi H, et al. *Abnormalities of neurohormonal and cardiac autonomic nervous activities relate poorly to functional status in fontan patients*. Circulation. 2004;11017:2601–8

[15] Constantinoiu S, Bârlă R, Iosif C, Cociu L, Gîndea C, Hoară P, Bratu O, Ruşitoru L. *Difficulties in diagnosis and surgical treatment of a giant retroperitoneal lipoma*. Chirurgia 2009;104(3): 363-367; Diaconescu D, Stoian Pantea A, Socea L, Stanescu AM, Iancu M, Socea B, Pituru S, Bratu O, Diaconu C. *Hepatorenal Syndrome: A Review*. Archives of the Balkan Medical Union, 2018, 53(2), pag. 239-245; Socea B, Nica A, Bratu O, Diaconu C, Smaranda A, Socea L, Bertesteanu S, Dimitriu M, Carap A, Constantin V. *Incidental finding of a sigmoid intussusception associated with rectal prolapse-a case report*. Archives of the Balkan Medical Union, 53(1), 2018, p. 143-146; Socea B, Nica A, Smaranda C, Carâp A, Socea L, Dimitriu M, Bratu O, Moculescu C, Bertești eanu Ș, Constantin V. *Solitary cecum diverticulitis – A surprising diagnosis.* Archives of the Balkan Medical Union, 2017, 52(4), , p. 467-470

[16] Tulevski II, Groenink M, van Der Wall EE et al. *Increased brain and atrial natriuretic peptides in patients with chronic right ventricular pressure overload: correlation between plasma neurohormones and right ventricular dysfunction*. Heart. 2001;861:27–30

[17] Manea M, Marcu D, Pantea Stoian A, Gaman MA, Gaman AM, Socea B, Neagu TP, Stanescu AM, Bratu O, Diaconu C. *Heart failure with preserved ejection fraction and atrial fibrillation. A review*. Revista de chimie, 2018, 69(11): 4180-4184

[18] Davos CH, Davlouros PA, Wensel R et al. *Global impairment of cardiac autonomic nervous activity late after repair of tetralogy of Fallot*. Circulation. 2002;10612 Suppl 1:I69–75

[19] Tulevski II, Groenink M, van Der Wall EE et al. *Increased brain and atrial natriuretic peptides in patients with chronic right ventricular pressure overload: correlation between plasma neurohormones and right ventricular dysfunction*. Heart. 2001;861:27–30

[20] Morgan C, Mohammed Al-Aklabi, Gonzalo Garcia Guerra. *Chronic kidney disease in congenital heart disease patients: a narrative review of evidence*. Canadian Journal of Kidney Health and Disease. 2015; 2:27

[21] Le Jemtel TH, Rajapreyar I, Selby MG et al. *Direct evidence of podocyte damage in cardiorenal syndrome type 2: preliminary evidence*. Cardiorenal Med. 2015;52:125–34

conducted by Agras et al., based on 43 patients with cyanotic heart disease, was found increased levels of sodium excretion and, also, an increased level of a marker of renal tubular damage[22].

Data from a recent study conducted on 1102 patients diagnosed with cyanotic and non-cyanotic congenital heart disease, has found that 50% of patients had decreased GFR[23]. So, patients with non-cyanotic heart disease have high risk to develop CKD, not just patients with cyanotic heart disease.

Shaw et al. found that children with congenital heart disease present anomalies in the renal function, 6 out of 11 children requiring dialysis after 5 years of progression of kidney injury. Also, this study observed not only decreased GFR, but elevated GFR, with hyperfiltration found in 36% of cases, which means early renal dysfunction[24].

Patients with congenital heart disease and renal dysfunction have a poor outcome. A study conducted on congenital heart disease patients established that CKD is an important predictor of mortality[25]. Also, children with congenital heart disease and CKD have atherosclerosis at an early age and vessel calcification. Also, in the young adults with congenital heart disease and CKD was observed endothelial dysfunction, associated with hypertension, cardiovascular events such as myocardial infarction and left ventricle hypertrophy[26]. Also, in these cases was observed increased coronary artery calcification and increased carotid intima-media thickness[27].

THERAPEUTIC STRATEGY AND KIDNEY INJURY

Cardiac surgery leads to kidney injury, a complication that appears due to ischemia-reperfusion. Acute kidney injury appears in 20-30% of children undergoing cardiac surgery.

Kidney injury after cardiac surgery is associated with a negative outcome, with endothelial damage, tubulointerstitial fibrosis and vascular changes[28].

Drugs used for congenital heart disease are nephrotoxic. Angiotensin-converting enzyme inhibitors are used to balance single-ventricle circulation, to prevent ventricular remodeling and

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[22] Toth R, Breuer T, Cserep Z et al. *Acute kidney injury is associated with higher morbidity and resource utilization in pediatric patients undergoing heart surgery*. Ann Thorac Surg. 2012;936:1984–90

[23] Parikh CR, Devarajan P, Zappitelli M et al. *Postoperative Biomarkers Predict Acute Kidney Injury and Poor Outcomes after Pediatric Cardiac Surgery*. J Am Soc Nephrol. 2011;229:1737–47

[24] Li S, Krawczeski CD, Zappitelli M et al. *Incidence, risk factors, and outcomes of acute kidney injury after pediatric cardiac surgery: a prospective multicenter study*. Crit Care Med. 2011;396:1493–9

[25] Manea M, Marcu D, Pantea Stoian A, Gaman MA, Gaman AM, Socea B, Neagu TP, Stanescu AM, Bratu O, Diaconu C. *Heart failure with preserved ejection fraction and atrial fibrillation. A review*. Revista de chimie, 2018, 69(11): 4180-4184

[26] Morgan CJ, Zappitelli M, Robertson CM et al. *Risk factors for and outcomes of acute kidney injury in neonates undergoing complex cardiac surgery*. J Pediatr. 2013;1621:120–7

[27] Sethi SK, Goyal D, Yadav DK et al. *Predictors of acute kidney injury post-cardiopulmonary bypass in children*. Clin Exp Nephrol. 2011;154:529–34

[28] Aydin SI, Seiden HS, Blaufox AD et al. *Acute kidney injury after surgery for congenital heart disease*. Ann Thorac Surg. 2012;945:1589–95; Paraschiv B, Dediu G, Iancu A, Bratu O, Diaconu C. *Superior vena cava syndrome*. Archives of the Balkan Medical Union, 2017, 52(1), p. 39-43; Mititelu R, Bratu O. *Radionuclide Imaging. An Update on the Use of Dynamic Renal Scintigraphy*. Modern Medicine, 2017, 24(4), p. 199-203; Niculae A, Peride I, Vinereanu V, Rădulescu D, Bratu O, Geavlete B, Checheriță IA. *Nephrotic syndrome secondary to amyloidosis in a patient with monoclonal gammopathy with renal significance (MGRS)*. Rom J Morphol Embriol 2017;58(3): 1065-1068

to control blood pressure. A retrospective study conducted on 206 hospitalised children diagnosed with congenital heart disease and treated with angiotensin-converting enzyme inhibitors, observed a decreased renal function and 42% of them presented kidney injury[29]. On the other hand, another study conducted on 319 children with congenital heart disease and treated with angiotensin-converting enzyme inhibitors, showed no kidney injury[30].

Other class of drugs used in patients with congenital heart disease are diuretics. Loop diuretics may affect renal blood flow, resulting in hypoperfusion due to vasodilation and diuresis. Moffett et al noticed that loop diuretics predispose to kidney injury after cardiac surgery[31].

TRANSITION FROM KIDNEY INJURY TO CHRONIC KIDNEY DISEASE IN CONGENITAL HEART DISEASE

Adults with congenital heart disease present kidney injury that progresses to chronic kidney disease[32]. In a study conducted by Mammen et al. on 126 patients with congenital heart disease, was noticed that after 3 years of progression of kidney injury, 10% of patients developed CKD[33].

Transition from kidney injury to CKD in patients with congenital heart disease is predisposed by cardiac surgery and by use of nephrotoxic drugs.

The diagnosis of kidney injury should be made early in order to prevent the progression to CKD[34].

CONCLUSION

Congenital heart diseases are highly associated with CKD, because of the pathophysiological changes that predispose to anomalies in the renal structure and function. The

[29] Basile DP, Friedrich JL, Spahic J et al. *Impaired endothelial proliferation and mesenchymal transition contribute to vascular rarefaction following acute kidney injury*. Am J Physiol Renal Physiol. 2011;3003:F721–33

[30] Lindle KA, Dinh K, Moffett BS et al. *Angiotensin-converting enzyme inhibitor nephrotoxicity in neonates with cardiac disease*. Pediatr Cardiol. 2014;353:499–506

[31] Phelps CM, Eshelman J, Cruz ED et al. *Acute kidney injury after cardiac surgery in infants and children: evaluation of the role of angiotensin-converting enzyme inhibitors*. Pediatr Cardiol. 2012;331:1–7

[32] Niculae A, Peride I, Marinescu-Paninopol A, Vrabie CD, Ginghină O, Jecan CR, Bratu OG. *Renal artery bilateral arteriosclerosis cause of resistant hypertension in hemodialysed patients*. Rom J Morphol Embriol 2016; 57(2): 591-594; Draghici T, Negreanu L, Bratu O, Tincu R, Socea B, Iancu M, Stanescu AM, Diaconu C. *Liver abnormalities in patients with heart failure*. Archives of the Balkan Medical Union, 2018, 53(1), p. 76-81

[33] Moffett BS, Goldstein SL, Adusei M et al. *Risk factors for postoperative acute kidney injury in pediatric cardiac surgery patients receiving angiotensin-converting enzyme inhibitors*. Pediatr Crit Care Med. 2011;125:555–9

[34] Veronica Calborean, Victor Gheorman, Vlad-Dumitru Baleanu et al. Arrhythmia risk in pacients with chronic disease. Revista de Chimie. 2018; 69(11): 3337-3340; Diaconu CC, Manea M., Iancu MA, Stanescu AMA, Socea B, Spinu DA, Marcu D, Bratu OG. *Hiponatremia in patients with heart failure: a prognostic marker*. Revista de Chimie. 2018. 69; 5:1071-1074; Diaconu CC, Stănescu AMA, Pantea Stoian A, Tincu RC, Cobilinschi C, Dragomirescu RIF, Socea B, Spînu DA, Marcu D, Socea LI, Bratu OG. *Hyperkalemia and cardiovascular diseases: new molecules for the treatment*. Rev Chim (Bucharest) 2018, 69(6):1367-1370; Diaconu CC, Dragoi CM, Bratu OG, Neagu TP, Pantea Stoian A, Cobelschi PC, Nicolae AC, Iancu MA, Hainarosie R, Stanescu AMA, Socea B. *New approaches and perspectives for the pharmacological treatment of arterial hypertension*. Farmacia 2018, 66(3):408-415

risk of appearance of CKD is higher in patients with cyanotic congenital heart disease, but it is also present in cases of non-cyanotic heart disease. Also, cardiac surgery for the correction of the cardiac lesion can lead to kidney injury, that can predispose to CKD if it remains undiagnosed. As nowadays patients undergo reparative correction of the cardiac defect early in life, it is not known if the risk of CKD remain the same over time.

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REFERENCES

1. **Baumgartner H., Bonhoeffer P., De Groot N et al.** *ESC Guidelines for the management of grown-up congenital heart disease*. European Heart Journal. 2010;31:2915-2957
2. **Marelli AJ, Mackie AS, Ionescu-Ittu R et al.** *Congenital heart disease in the general population: changing prevalence and age distribution*. Circulation. 2007;1152:163–72.
3. **Billett J, Cowie MR, Gatzoulis MA et al.** *Comorbidity, healthcare utilisation and process of care measures in patients with congenital heart disease in the UK: cross-sectional, population-based study with case-control analysis*. Heart. 2008;949:1194–9.
4. **Cordina RL, Celermajer DS**. *Chronic cyanosis and vascular function: implications for patients with cyanotic congenital heart disease*. Cardiol Young. 2010;203:242–53.
5. **DeFilippis AP, Law K, Curtin S, Eckman JR**. *Blood is thicker than water: the management of hyperviscosity in adults with cyanotic heart disease*. Cardiol Rev. 2007;151:31–4.
6. **Perloff JK, Latta H, Barsotti P**. *Pathogenesis of the glomerular abnormality in cyanotic congenital heart disease*. Am J Cardiol. 2000;8611:1198–204.
7. **Morgan C, Mohammed Al-Aklabi, Gonzalo Garcia Guerra**. *Chronic kidney disease in congenital heart disease patients: a narrative review of evidence*. Canadian Journal of Kidney Health and Disease. 2015; 2:27
8. **Ohuchi H, Takasugi H, Ohashi H, et al**. *Abnormalities of neurohormonal and cardiac autonomic nervous activities relate poorly to functional status in fontan patients*. Circulation. 2004;11017:2601–8.
9. **Constantinoiu S, Bârlă R, Iosif C, Cociu L, Gîndea C, Hoară P, Bratu O, Ruşitoru L**. *Difficulties in diagnosis and surgical treatment of a giant retroperitoneal lipoma*. Chirurgia 2009;104(3): 363-367.
10. **Diaconescu D, Stoian Pantea A, Socea L, Stanescu AM, Iancu M, Socea B, Pituru S, Bratu O, Diaconu C**. *Hepatorenal Syndrome: A Review*. Archives of the Balkan Medical Union, 2018, 53(2), pag. 239-245.
11. **Socea B, Nica A, Bratu O, Diaconu C, Smaranda A, Socea L, Bertesteanu S, Dimitriu M, Carap A, Constantin V**. *Incidental finding of a sigmoid intussusception associated with rectal prolapse-a case report*. Archives of the Balkan Medical Union, 53(1), 2018, p. 143-146.
12. **Socea B, Nica A, Smaranda C, Carâp A, Socea L, Dimitriu M, Bratu O, Moculescu C, Berteșteanu Ș, Constantin V.** *Solitary cecum diverticulitis – A surprising diagnosis.* Archives of the Balkan Medical Union, 2017, 52(4), , p. 467-470.
13. **Tulevski II, Groenink M, van Der Wall EE et al**. *Increased brain and atrial natriuretic peptides in patients with chronic right ventricular pressure overload: correlation between plasma neurohormones and right ventricular dysfunction*. Heart. 2001;861:27–30.
14. **Manea M, Marcu D, Pantea Stoian A, Gaman MA, Gaman AM, Socea B, Neagu TP, Stanescu AM, Bratu O, Diaconu C**. *Heart failure with preserved ejection fraction and atrial fibrillation. A review*. Revista de chimie, 2018, 69(11): 4180-4184
15. **Davos CH, Davlouros PA, Wensel R et al.** *Global impairment of cardiac autonomic nervous activity late after repair of tetralogy of Fallot*. Circulation. 2002;10612 Suppl 1:I69–75.
16. **Le Jemtel TH, Rajapreyar I, Selby MG et al.** *Direct evidence of podocyte damage in cardiorenal syndrome type 2: preliminary evidence*. Cardiorenal Med. 2015;52:125–34.
17. **Toth R, Breuer T, Cserep Z et al**. *Acute kidney injury is associated with higher morbidity and resource utilization in pediatric patients undergoing heart surgery*. Ann Thorac Surg. 2012;936:1984–90.
18. **Parikh CR, Devarajan P, Zappitelli M et al.** *Postoperative Biomarkers Predict Acute Kidney Injury and Poor Outcomes after Pediatric Cardiac Surgery*. J Am Soc Nephrol. 2011;229:1737–47.
19. **Li S, Krawczeski CD, Zappitelli M et al.** *Incidence, risk factors, and outcomes of acute kidney injury after pediatric cardiac surgery: a prospective multicenter study*. Crit Care Med. 2011;396:1493–9.
20. **Morgan CJ, Zappitelli M, Robertson CM et al**. *Risk factors for and outcomes of acute kidney injury in neonates undergoing complex cardiac surgery*. J Pediatr. 2013;1621:120–7.
21. **Sethi SK, Goyal D, Yadav DK et al**. *Predictors of acute kidney injury post-cardiopulmonary bypass in children*. Clin Exp Nephrol. 2011;154:529–34.
22. **Aydin SI, Seiden HS, Blaufox AD et al**. *Acute kidney injury after surgery for congenital heart disease*.

Ann Thorac Surg. 2012;945:1589–95.
23. **Paraschiv B, Dediu G, Iancu A, Bratu O, Diaconu C.** *Superior vena cava syndrome*. Archives of the Balkan Medical Union, 2017, 52(1), p. 39-43.
24. **Mititelu R, Bratu O**. *Radionuclide Imaging. An Update on the Use of Dynamic Renal Scintigraphy*. Modern Medicine, 2017, 24(4), p. 199-203.
25. **Niculae A, Peride I, Vinereanu V, Rădulescu D, Bratu O, Geavlete B, Checheriță IA**. *Nephrotic syndrome secondary to amyloidosis in a patient with monoclonal gammopathy with renal significance (MGRS)*. Rom J Morphol Embriol 2017;58(3): 1065-1068.
26. **Basile DP, Friedrich JL, Spahic J et al.** *Impaired endothelial proliferation and mesenchymal transition contribute to vascular rarefaction following acute kidney injury*. Am J Physiol Renal Physiol. 2011;3003:F721–33.
27. **Lindle KA, Dinh K, Moffett BS et al**. *Angiotensin-converting enzyme inhibitor nephrotoxicity in neonates with cardiac disease*. Pediatr Cardiol. 2014;353:499–506.
28. **Phelps CM, Eshelman J, Cruz ED et al**. *Acute kidney injury after cardiac surgery in infants and children: evaluation of the role of angiotensin-converting enzyme inhibitors*. Pediatr Cardiol. 2012;331:1–7.
29. **Niculae A, Peride I, Marinescu-Paninopol A, Vrabie CD, Ginghină O, Jecan CR, Bratu OG**. *Renal artery bilateral arteriosclerosis cause of resistant hypertension in hemodialysed patients*. Rom J Morphol Embriol 2016; 57(2): 591-594.
30. **Draghici T, Negreanu L, Bratu O, Tincu R, Socea B, Iancu M, Stanescu AM, Diaconu C**. *Liver abnormalities in patients with heart failure*. Archives of the Balkan Medical Union, 2018, 53(1), p. 76-81.
31. **Moffett BS, Goldstein SL, Adusei M et al**. *Risk factors for postoperative acute kidney injury in pediatric cardiac surgery patients receiving angiotensin-converting enzyme inhibitors*. Pediatr Crit Care Med. 2011;125:555–9.
32. **Veronica Calborean, Victor Gheorman, Vlad-Dumitru Baleanu et al.** Arrhythmia risk in pacients with chronic disease. Revista de Chimie. 2018; 69(11): 3337-3340.
33. **Diaconu CC, Manea M., Iancu MA, Stanescu AMA, Socea B, Spinu DA, Marcu D, Bratu OG**. *Hiponatremia in patients with heart failure: a prognostic marker*. Revista de Chimie. 2018. 69; 5:1071-1074
34. **Diaconu CC, Stănescu AMA, Pantea Stoian A, Tincu RC, Cobilinschi C, Dragomirescu RIF, Socea B, Spînu DA, Marcu D, Socea LI, Bratu OG**. *Hyperkalemia and cardiovascular diseases: new molecules for the treatment*. Rev Chim (Bucharest) 2018, 69(6):1367-1370.
35. **Diaconu CC, Dragoi CM, Bratu OG, Neagu TP, Pantea Stoian A, Cobelschi PC, Nicolae AC, Iancu MA, Hainarosie R, Stanescu AMA, Socea B**. *New approaches and perspectives for the pharmacological treatment of arterial hypertension*. Farmacia 2018, 66(3):408-415.