

REVIEW

From prof. Dr. Anna Ivanova Kaneva-Nencheva PhD,

Head of Pediatric Cardiology Clinic

at the National Cardiology Hospital – EAD

Member of the scientific jury, appointed by order № 447/30.10.2024 of Dr. Krasimir Dzhinov, CEO of NKB Hospital EAD, according to the decision of the Scientific Council (protocol No. 18 of 08.10.2024) in the competition for the academic position of "Associate Professor" in the field of higher education 7. "Health and Sport", professional field "Medicine" in the scientific specialty "Pediatric Cardiology" for the needs of the Clinic of Pediatric Cardiology, announced in SG No. 91/29.10.2024

This opinion has been prepared following the Academic Staff Development Act of the Republic of Bulgaria, the Regulations for the Application of the Academic Staff Development Act, and the Regulations of the NQB on the Conditions and Procedure for the Acquisition of the Academic Position "Associate Professor".

I have no conflict of interest in serving on this scientific panel.

For participation in the competition were submitted documents by a single candidate Dr. Zornitsa Nikolova Vassileva-Enikova.

Professional and career development. Dr. Zornitsa Vassileva graduated in medicine in 2005 at the Medical University, Sofia. In the period 2006-2013, she was an assistant professor at the Hospital of Medical and Dental Sciences. Between 2012 and 2019 Dr. Vassileva worked in Belgium as a pediatrician in Lokeren and a consultant in pediatric cardiology at Ghent University Hospital. Since 2019 she has been appointed as assistant professor at the Clinic of Paediatric Cardiology of the National Cardiology Hospital and since 2023 she has been senior assistant professor.

Dr. Vassileva has three specialties – general pediatrics (2007), pediatric cardiology (2017), and health management (2022). She has a professional qualification certificate in pediatric echocardiography - fundamental level (2019), and fetal echocardiography (2021). She also has a European certificate in echocardiography from 2018.

In February 2023 Dr. Vassileva successfully defended her dissertation on "Preoperative echocardiographic diagnosis of complete atrioventricular septal defect".

Dr. Vassileva is fluent in English and Dutch and at a basic level in French, German and Russian.

Dr. Vassileva actively participates in the training of pediatric cardiology fellows, the pediatric cardiology module of pediatrics, neonatology, pediatric subspecialties, and cardiac surgery. She is the supervisor of 2 pediatric cardiology specialty fellows. As a visiting assistant professor at the Medical University of Sofia Dr. Vassileva participates in the teaching activity of medical students in the 5th year, module "Pediatric Cardiology" from "Pediatrics" curriculum in Bulgarian and English. The average teaching load for the last 5 years is over 250 hours/year.

Research. Dr. Vassileva participated in the competition with a dissertation, three publications related to the dissertation, an independent monograph, 88 real publications (8 in journals with impact factor, 14 refereed and indexed in the world database, 22 published in the national reference list and 44 in non-refereed journals. Five abstracts of research papers were published in impact factor journals and 2 abstracts were published in refereed journals. In 85 of the submitted publications, Dr Vassileva is the first or sole author, in 2 - second, and in the remaining 11 third or subsequent author.

In the submitted reference from the Central medical library, Dr Vassileva's publications are cited in 8 Bulgarian and 16 foreign sources (3 in Scopus, 9 in Web of Science, and 4 in freely available online sources). The total Impact Factor is 8,051.

Dr. Zornitsa Vassileva's **research interests** are broad and include various aspects of pediatric cardiology - congenital heart defects, inflammatory heart diseases, rhythm-conduction disorders, therapeutic strategies, as well as fetal medicine, cardiology, pediatrics, endocrinology, angiology, and vascular surgery, rare clinical cases

A major focus of Dr. Vassileva's publications is on atrioventricular septal defect (AVSD), a congenital heart defect (CHD) that is often combined with trisomy 21 (Down syndrome). This CHD is characterized by an extreme diversity of forms and clinical presentation- from "simple" VSD with a left-to-right shunt to cases with the early development of pulmonary obstructive vascular disease and adverse outcome; from patients with a successful biventricular surgical correction to unbalanced forms with single-ventricle hemodynamics and the possibility of only Fontan-type functional corrections. Echocardiography is the main method of diagnosis, setting the indications for correction and monitoring the natural and postoperative evolution. In Dr. Vassileva's dissertation "Preoperative echocardiographic diagnosis of complete atrioventricular septal defect" an ambispective analysis of 100 consecutive patients with AVSD, 86 with balanced and 14 with unbalanced form was performed. Based on systematic echocardiographic measurements, 4 echocardiographic parameters were defined- AV valve index, angle of inflow to the ventricles, inflow to the mitral valve, and long axes of both ventricles, which allowed

differentiation of balanced from imbalanced forms. Based on these, a scoring system was developed which had a positive predictive value of 97%.

A logical continuation of the dissertation work of Dr. Zornitsa Vassileva is the monograph "Atrioventricular septal defect- embryology, prenatal diagnosis, hemodynamics, anatomical characteristics, natural and postoperative evolution, echocardiographic evaluation" published in 2024, which presents the current knowledge and guidelines for the diagnosis, management and follow-up of this complex CHD. The monograph systematically, consistently, and thoroughly presents the incidence, genetics, embryology, anatomic characterization and classification of AVSD, prenatal diagnosis, and hemodynamic evaluation based on an extensive literature review. The main focus is on preoperative echocardiography with assessment of balance, complex forms, and therapeutic approaches in different forms of AVSD, partial and complete, balanced and unbalanced. Postoperative echocardiographic evaluation is discussed in detail, as well as the management of adults and pregnant women with AVSD. Dr. Vassileva's monograph, in which a highly complex subject is presented in accessible language, with precise and clear definitions and messages, and which is extremely well illustrated, fills a gap in the medical literature in this country and will be of value to pediatric cardiologists, pediatricians, neonatologists, cardiologists, cardiac surgeons, fellows, and all those with an interest in congenital heart disease.

In Dr. Vassileva's publications, which summarize data from her own studies, those treating the problems of infective endocarditis, the complications of Covid 19 in childhood, fetal medicine and critical cardiopathies, risk assessment after cardiac surgery, and rare clinical cases stand out.

Infective endocarditis

Infective endocarditis (IE) is one of the most ominous diseases in any age and is characterized by high morbidity and mortality. Dr. Vassileva analyzed the factors influencing the outcome in IE of 20 patients under the age of 18 years with underlying VSM hospitalized at Children's Cardiology Clinic in the period 2009-2022. The diagnosis was delayed by more than 30 days in 40% of the children and 60% had received prior antibiotic therapy. Surgery was performed in 60%. Fatality occurred in 3 children, all with prior empiric therapy. According to current recommendations, a diagnosis based on positive hemoculture and visualization of vegetations on echocardiographic examination should be excluded in any child with known cardiac disease and persistent febrility. Prerequisites for a favorable outcome are timely etiologic diagnosis, early initiation of antibiotic therapy, and subsequent

surgical treatment. Empiric antibiotic therapy is associated with delay in etiologic diagnosis, and delay in surgery adversely affects outcome.

Dr. Vassileva published an interesting clinical case of an infant weighing 3.9 kg without underlying cardiopathy who developed candidal endocarditis, in whom after an initial valve-sparing operation, due to recurrence of endocarditis, the smallest possible mitral valve prosthesis - 16 mm - was successfully placed at the second stage.

The spectrum of childhood IE in operated and non-operated patients was presented at a national congress of cardiology.

The problems of IE and the current recommendations of the European Society of Cardiology for diagnosis, treatment, and prevention are presented at a national congress of pediatrics.

Complications of Covid 19.

Throughout the 2019-2021 COVID-19 pandemic, an increase in cases of children of various age groups with symptoms of multisystem inflammation, often in combination with circulatory failure and myocarditis and exposure to SARS-CoV2, has been reported in the global literature. The constellation of symptoms has been termed multisystem inflammatory syndrome in children MIS-C. In two publications, Dr. Vassileva presents data from retrospectively pooled cases of children hospitalized and treated in the pediatric cardiology clinic. Demographic characteristics, clinical presentation with 100% cardiac involvement, ECG, X-ray, Echocardiogram, and in 6 children MRI data are presented. Laboratory investigations showed high inflammatory activity, thrombocytosis, high levels of D-dimers, highly elevated troponins, and BNP. High doses of intravenous immunoglobulin were administered in the treatment of all children, resulting in a positive effect on the clinical symptoms, laboratory parameters, and ECG. Although there are no exact statistics of children with MIS-C in our country, these 10 children are probably representative of the country for severe cardiac involvement. The conclusions drawn by Dr. Vassileva are consistent with the international ones: cardiac involvement in COVID-19 is immune-mediated and immunomodulatory therapy is the mainstay of treatment; dramatic improvement in clinical status, laboratory and ultrasonographic findings was observed 48-72 hours after administration of intravenous immunoglobulin therapy; troponin is a specific laboratory marker of myocardial involvement; MRI is the leading test for the diagnosis of myocardial involvement as MRI changes are detected against a background of normal echocardiographic examination and persist to varying degrees in individual patients at the sixth month. The long-term prognosis remains unclear.

The author describes a case of transient complete AV block in a child with multisystem inflammatory syndrome in whom emergency placement of a temporary pacemaker was necessary.

Issues related to the Kovid pandemic and MIS-C are also addressed in 3 review publications.

Critical Cardiopathies and Fetal Medicine

Prenatal diagnosis is important for proactive management of CHD - counseling families, identifying fetuses at risk for critical CHD requiring treatment in the neonatal period, determining the site for delivery, and possibly advising termination of pregnancy when evidence of complex CHD is present. Worldwide, in countries with well-organized prenatal medicine, the fetal diagnosis of CHD is as high as 60%. Dr. Vassileva retrospectively analyzed 194 children with critical CHD hospitalized in the pediatric cardiology clinic between 2015 and 2019 and demonstrated that only 15% had a prenatally established diagnosis. The diagnosis was also missed in children with complex CHD of common ventricle type. Delay in diagnosis in children with duct-dependent CHD such as critical coarctation of the aorta or pulmonary atresia on the other hand leads to delay in prostaglandin treatment and puts the children at risk. The suboptimal detection of critical CHD found by Dr. Vassileva necessitates expanding the indications of prenatal echocardiography, training specialists, deepening contacts with obstetricians, and creating a unified registration system.

As a logical continuation, the recommendations for fetal echocardiography are presented in review articles and the indications for the study, the possibilities and limitations of the method are described in detail.

Interesting cases have been published with pathological abnormalities on fetal echocardiography- of arterial duct constriction caused by SSRIs, necessitating strict medication control in pregnant women with depression, and of transient fetal nonimmune grade 2 AV block.

Risk assessment after cardiac surgery.

Dr. Vassileva is part of the team that developed risk assessment systems after heart surgery.

One of them is the analysis of risk factors for prolonged invasive pulmonary ventilation (PIPV) and the creation of a prognostic model allowing proactive detection of patients at risk. Vasoactive ventilatory scoring (VVS) analysis, which allows the assessment of 3 systems, cardiovascular, respiratory, and renal, was studied in the first 48 hours after cardiac surgery in 438 patients divided into 2 groups. A peak BBBS value above 38.84 on

the day of surgery had a sensitivity of 82% and a specificity of 84%, making it a reliable predictor of the need for PIBV and the outcome of cardiac surgery.

One of the modern risk assessment scales, created in Boston and used in our country, is based on the type of cardiac malformation. RACHS-1 (Risk Adjustment in Congenital Heart Surgery) divides them into 6 groups, with risk being directly proportional to severity. In an analysis of the operative mortality of 438 operated children, early operative mortality was shown to increase statistically significantly with increasing severity from 1 to 6. The system is easy to implement and highly effective in terms of predicting operative mortality. It allows for comparison of outcomes at different time intervals, both within an institution and between institutions.

Cassius occupy a substantial part of the publications presented. Some of them are mentioned in the headings above. In addition, the following are described: a case of cerebral venous thrombosis in a child after otitis, overcome by oral anticoagulant treatment; a case of retroperitoneal aorto-femoral bypass in a patient with horseshoe kidney and aorto-iliac occlusive disease with stent thrombosis in the iliac artery; infrarenal aortic dissection with lower limb ischemia; cases with carotid artery pathology including elongation and kinking and with a migrated stent.

Dr. Vassileva presents in the form of **reviews, consensuses, modern recommendations** on various aspects of diagnosis, treatment, and follow-up in children and adults, intended for pediatricians, pediatricians, cardiologists, general practitioners. In the field of pediatric cardiology, rhythm-conduction disorders, cardiomyopathies in childhood, an algorithm for predicting sudden cardiac death in children with hypertrophic cardiomyopathy, diagnostic and therapeutic approach to syncope, pulmonary arterial hypertension, recommendations for cardiac catheterization, indications for magnetic resonance imaging, cardiac risk assessment in non-cardiac surgery are presented. Special attention is given to current recommendations for the treatment of venous thrombosis and the use of new direct anticoagulants in children. Of interest to cardiologists are various aspects of CHD in adults such as a review of the European Society of Cardiology recommendations from 2020, AVSD, and right ventricular outflow tract obstructions in adults. Cardiovascular complications of Kawasaki disease, cardiovascular risk in patients with type 2 diabetes and advanced age, and recommendations for the management of atrial fibrillation are presented. Publications for general practitioners are devoted to tetralogy of Fallot, CHD in trisomy 21, prenatal diagnosis of CHD, and new developments in Kawasaki disease. Several reviews treat various aspects of the diagnosis, treatment, and complications of diabetes in children.

Scientific activity. Dr. Vassileva presents a list of 27 participations in national and international conferences and congresses, 7 of them with published abstracts in national and international journals, and is the first author in 25 of them.

Dr. Zornitsa Vassileva is a member of the Society of Cardiologists in Bulgaria, the Bulgarian Pediatric Association, and the European Association for Paediatric and Congenital Cardiology, Children's Heart Association. She is a consultant to the charity initiative "Bulgarian Christmas"

According to the attached reference and the tables for the fulfillment of the National Minimum Science Metric Criteria, Dr. Zornitsa Nikolova Vassileva-Enikova exceeded many times the required group-wise indicators for the mandatory and specific conditions for holding the academic position of Associate Professor.

Table. Scientific metrics for Dr. Zornitsa Vassileva

	LINK	Minimum number of points	Implemented number of points
A	Indicator 1	50	50
B	Indicator 3 and 4	100	100
C	Sum of indicators 5 to 9	200	961.89
D	Sum of indicators 10 to 12	50	60
E	Sum of indicators from 13 to the end		
	TOTAL	400	1076

With her scientific developments, Dr. Zornitsa Vassileva has contributed to the development of the specialty "Pediatric Cardiology" at the Hospital "NKB" EAD and the establishment of its prestige in Bulgaria.

As an **original contribution**, for the first time in Bulgaria, a systematic analysis of the preoperative echocardiographic findings in patients with AVSD was performed and a scoring system of echocardiographic poses was created, which allows differentiating balanced from unbalanced AVSD.

The scientific and applied contributions are related to the analysis of the clinical presentation and prognosis of infective endocarditis and multisystem inflammatory syndrome after infection with COVID-19, the prenatal diagnosis of critical CHD, and the introduction of risk assessment systems after cardiac surgery.

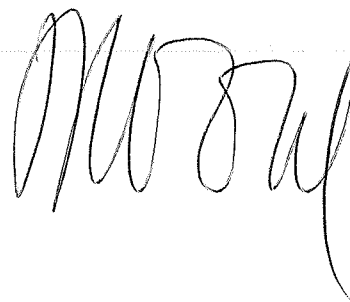
The team-based **multidisciplinary approach** to the diagnosis and treatment of complex and rare structural cardiopathies and vascular anomalies is well-established.

Recommendations for the management of venous thromboembolism, syncope, rhythm and conduction disorders, diagnosis, and treatment of adults with CHD are presented

In conclusion, Dr. Zornitsa Nikolaeva Vassileva-Enikova is a thorough scientist with diverse scientific interests, extensive clinical experience, and a taste for new developments in structural echocardiography and fetal echocardiography, for the most problematic aspects of pediatric cardiology and medical science. She is one of the leading pediatric cardiologists in the country and enforces the European team principle in clinical and scientific work. All this gives me the reason to confidently give a positive evaluation for the position of academic associate professor.

Sofia, 01.03.2024

Prof. Anna Kaneva-Nencheva MD

A handwritten signature in black ink, appearing to read 'Anna Kaneva-Nencheva', written in a cursive style.