Abstract of Habilitation Thesis

CLINICAL RESEARCH IN NEONATOLOGY AND NEONATAL ULTRASOUND - PRESENT AND FUTURE

Cucerea Manuela-Camelia

The habilitation thesis is the corollary of my professional, academic, and scientific work, conducted throughout my career following the attainment of the Doctor of Medicine title on January 30, 2004. This was confirmed by the Ministry of Education and Research through Order no. 3876/19.05.2004, M.E.C. (Diploma series D, no. 0003755).

In 1988, I graduated as the top student from the University of Medicine and Pharmacy in Târgu Mureș. After receiving a recommendation for research activity from the University's Faculty Council, I started my career in challenging conditions after 1990. I contributed significantly to the birth and development of Neonatology, the most rapidly advancing medical specialty in Romania. With specializations in pediatrics and neonatology and certification as a senior doctor in both fields, I have a comprehensive understanding of newborn care. I acquired proficiency in General Ultrasonography in 2008, and currently, I am nationally responsible for obtaining the Certificate of complementary training in Head Ultrasound (O.M.S. no. 12 of 16.02.2023).

I have been involved in significant projects to advance Neonatology, including NEWSTART I-IV (a Romanian American program) and RoNeoNat (a Romanian-Swiss program). As a result, I became the coordinator of the Regional Neonatal Intensive Care Center in Târgu Mureș, which was one of the first two pilot centers in Romania in 2004. I participated in neonatal intensive care training at Kosair Children's Hospital in the Neonatology Department/Neonatology Intensive Care, University of Louisville, Kentucky, USA. Additionally, I received training in follow-up and quality management in neonatology at Hopitaux Universitaires de Geneve, Swiss Center for International Health: MDK Alzey in Germany, SCIH in Basel, and Outcome Verein in Zurich, Switzerland.

My academic activity started in 1999, and I am currently an Associate Professor. I have supervised 47 bachelor's theses and 7 master's theses, and I am a specialist advisor for 18 doctoral theses. I have authored and co-authored over 23 specialized books, and I coordinate and review the National Neonatology Guidelines.

I based my habilitation thesis on 29 published ISI articles with impact factors and participation in international studies. Hirsch Index = 6, FCIP = 25.4. My main achievements and contributions to the development of the field of neonatology focus on the management of respiratory distress syndrome due to surfactant deficiency, neonatal resuscitation, extreme prematurity, assisted ventilation, preoperative management of critical congenital heart malformations, and neonatal ultrasound.

One of the most important research topics was the management of surfactant deficiency respiratory distress syndrome (RDS), particularly the etiological treatment with surfactant and the study of ABCA3 polymorphisms in premature newborns with a gestational age of less than 32 weeks. The Regional Neonatal

Intensive Care Center of Târgu-Mureș was among the first centers in Romania to administer exogenous surfactant (1999), initially by the classic method of intubation followed by mechanical ventilation. We promptly adopted minimally invasive surfactant administration methods (LISA/MIST/NIST) following the new international guidelines for managing respiratory distress syndrome. In 2013, we became pioneers in Romania for the LISA technique and conducted the first Romanian study on surfactant administration methods. The study enrolled 135 premature infants with a gestational age between 220/7 and 316/7 weeks and with RDS. They benefited from surfactant administration using three different methods. The study demonstrated that the LISA method is safe and does not involve major risks when the necessary skills and experience are present. This method reduces the need for invasive ventilatory support and positively affects the subsequent evolution, as demonstrated by similar studies.

I was the national representative in a European study of UENPS involving 397 intensive care units from 37 European countries. The study focused on respiratory management strategies for premature newborns. The survey results show that these strategies align with the latest international guidelines. However, there are some differences in terms of the viability threshold (22 vs. 24 gestational weeks), the use of sustained lung inflations in resuscitation, the CO_2 detector, the laryngeal mask, premedication before minimally invasive surfactant administration, and the incidence of BPD. In addition to treating RDS, there has been significant research interest in minimally invasive ventilation. It is a challenge for every neonatologist to choose a non-invasive ventilation mode tailored to each patient to ensure optimal ventilatory support. Thus, we conducted a multicenter study in Romania (18 level III centers) on the implementation of high-frequency nasal oscillatory ventilation (nHFOV) as the initial mode of rescue ventilation for premature newborns with RDS. The study revealed the neonatologists' adherence to this ventilation mode in Romania but also identified a need for training courses.

Another personal concern was the study of the transition to extrauterine life and the implementation in the everyday practice of the two new concepts in neonatology: the “Golden Minute” (an opportunity for the establishment of spontaneous breathing) and the “Golden Hour." Neonatal resuscitation, post-resuscitation care, transportation of sick newborns to the neonatal intensive care unit, and respiratory and cardiovascular support are all part of these concepts. Timely intervention is crucial in ensuring a high quality of life for the individual in the future. In 2022, I took part in a European study on neonatal resuscitation practices based on a survey conducted by UENPS and ANR. The study considered 730 neonatal centers in Europe and showed some variations depending on the hospitals and geographic region. Centers in Europe generally implement clinical practices recommended by international guidelines, but there are discrepancies, especially in perinatal care. I have also conducted a study involving all regional level III centers in Romania, which served 42.66% of all births in Romania in the reference year 2018. The study results showed that 69.7% of level III maternity hospitals perform delayed clamping of the umbilical cord for term newborns during vaginal delivery (comparable to the European study). Most centers utilize the T-piece resuscitator for CPAP and positive pressure ventilation. The initial FiO_2 is as per current international guidelines, specifically 21% for full-term neonates and 30% for preterm neonates with VG < 28 weeks. The UENPS study, to which I contributed, compared the use of the laryngeal mask to the face mask and intubation tube for neonatal

resuscitation. The study found that only 9% of European hospitals consider the laryngeal mask as their first choice for neonatal resuscitation. It is often considered the second choice after bag and mask ventilation (30%) or intubation tube (43%). However, the need to reassess the effectiveness of this interface was emphasized, highlighting the requirement for ongoing staff training.

My research has also focused on extreme prematurity and periviability. I conducted a retrospective study at NICU Tîrgu Mureș, comparing two different periods: January 1, 2008, to December 31, 2012, and January 1, 2018, to December 31, 2022. The study focused on resuscitation practices in the delivery room and early management of RDS in neonates with gestational age ≤ 28 weeks, in accordance with the guidelines and protocols implemented during the two separate 10-year periods of neonatology evolution. We developed a prediction model for mortality in the two study periods using multivariate Cox regression. During the first period of the study, factors such as low birth weight, lack of antenatal corticotherapy, postnatal transfer, severe intraventricular hemorrhage, and bronchopulmonary dysplasia contributed to a decreased survival rate. However, lung recruitment at birth and the administration of high doses of surfactant reduced the risk of death in the second period. As a result, the mortality rate decreased significantly from 41.3% in Period I to 27.5% in Period II.

We conducted a study on the early hematological profile of 159 extremely premature newborns to predict intraventricular hemorrhage. We found that cut-off values for hemoglobin < 13.9 g/dL, hematocrit < 42.6%, and erythrocyte count < 3.82 x 10^6/mm^3 at birth can be significant predictors for intraventricular hemorrhage. This information can be helpful in medical practice, allowing for early suspicion of intraventricular hemorrhage from birth.

The team of neonatologists from NICU Târgu Mureș has extensive experience in caring for newborns with critical congenital heart malformations, which has resulted in clinical studies on their preoperative management. We conducted a study on the use of PGE1 to treat neonates with critical ductal-dependent heart malformations. We conclude that treatment is essential, but it should be administered in appropriate therapeutic doses to avoid even transient side effects. The lowest therapeutically effective dose should be utilized, and the duration of treatment should be as brief as possible until surgical resolution. We also investigated the predictive value of SNAP-II, SNAPPE-II, and CRIB-II severity scores for respiratory support in neonates with transposition of great vessels and coarctation of the aorta. Research has also focused on prenatal diagnosis of heart defects with systemic blood flow restriction. The study revealed improved hemodynamic stability in newborns diagnosed antenatally.

Research in the field of Head Ultrasound began with doctoral studies. Starting from the subject of my doctoral thesis, which is the role of head ultrasound in diagnosing and monitoring brain conditions in newborns, I have strived to enhance my skills in this valuable technique continually. As the director of a grant won in 2020, I conducted a study to assess the predictive value of cerebral and splanchnic Doppler investigation in managing ductus arteriosus persistence in preterm neonates with a gestational age of less than 32 weeks. We also examined the impact of early surfactant administration on the ductus arteriosus at 24 hours of life. This study involving 88 preterm infants demonstrated that surfactant administration had a significant predictive power on clinical parameters of assessment of the ductus arteriosus but did not have a

significant impact on the sonographic parameters of the ductus arteriosus and cerebral and splanchnic arteries 24 hours after birth.

We utilized cerebral Doppler ultrasound and measured regional cerebral saturations using NIRS to examine the impact of prostaglandin E1 and balloon atrial septostomy on cerebral blood flow and oxygenation in neonates with transposition of the great arteries. The study emphasized the importance of carefully monitoring cerebral hemodynamics using Doppler ultrasound and cerebral saturations with NIRS for correct preoperative management. PGE1 treatment and atrial septostomy are life-saving interventions that can improve cerebral perfusion and oxygenation in neonates with the transposition of great arteries during their transition to extrauterine life.

In NICU Târgu Mureş, I introduced lung ultrasound as a complementary diagnostic method to chest radiography 5 years ago. I was a national representative for the European Society of Pediatric Research (ESPR) consortium in a European study on the use of this investigation in neonatal intensive care, involving 560 centers in 24 countries. The study concluded that lung ultrasound is becoming increasingly important in neonatology, and the implementation of this diagnostic method could be enhanced by creating a standardized curriculum and international guidelines for neonatologists.

The plan for advancing the teaching career involves developing the Training Center in Neonatology, with a focus on Head and Neonatal Lung Ultrasound in Târgu Mureş. It also includes training in simulators and expanding the national Telemedicine network in Neonatology. The upcoming research will focus on continuing neonatal ultrasound studies (POCUS), investigating the impact of red blood cell mass transfusion on hemodynamics and cerebral and mesenteric oxygenation in premature infants, evaluating General Movements Assessment (GMA) in premature newborns for developmental care, and participating in international multicenter studies (NEU-STIM, NEU-VODE).