UNIVERSITY OF MEDICINE AND PHARMACY "GRIGORE T POPA"
IASI, ROMANIA
FACULTY OF MEDICINE

HABILITATION THESIS

FACTS AND CHALLENGES IN NURSING AND INTERNAL MEDICINE

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2020

CONTENTS

REZUMAT

Sunt Conferenţiar universitar la Universitatea de Medicină şi Farmacie "Grigore T Popa" din Iaşi. Experienţa mea de medic însumează 34 de ani, iar cea de cadru didactic universitar 30.

Sunt medic specialist de medicină internă din 1994 şi medic primar din 1998.Sunt medic şef de secţie al Clinicii Medicale 1 a Spitalului Clinic Judeţean de urgenţă "Sf. Spiridon" din Iaşi din anul 2008. În perioada septembrie 1990 – Martie 2001 am fost cadru didactic asociat, asistent universitar pentru disciplina de medicină internă, predând la seriile de limbă engleză a anilor IV şi V a facultăţii de medicină. Din Ianuarie 2001 am ocupat prin concurs postul de şef de lucrări la disciplina nou înfiinţată de Nursing, pe care am dezvoltat-o. Am susţinut examenul de doctorat în 2002 cu teza "Infarctul miocardic de ventricul drept ca factor independent de prognostic al infarctului inferior acut", sub îndrumarea Profesorului Adrian Cosovanu la UMF Iaşi. Sunt Conferenţiar universitar din 2003.

Teza prezentă, intitulată "Facts and Challenges in Nursing and Internal Medicine", oferă o imagine sintetică şi de ansamblu a activităţii mele ştiinţifice, profesionale şi academice, cu scopul de a obţine calificarea de a îndruma student doctorali. Prezentarea este structurată în 3 secţiuni.

Prima secţiune ilustrează realizările mele ştiinţifice, profesionale şi academice şi conţine 3 capitole.

Introducerea prezintă o imagine global a dezvoltării traiectorii ca medic şi cadru didactic universitar şi explică interesul meu dublu în cercetare, în domeniul medicinii interne şi nursingului, oferind o privire asupra granturilor international la care am participat şi a progresului obţinut în carieră.

Primul capitol este dedicate nursingului, un domeniu fundamental în continuumul îngrijirilor de sănătate. Cuprinde un review asupra locului şi importanţei nursingului în contextual demographic actual, al schimbărilor şi provocărilor existente, care implică schimbarea rolurilor profesionale ale asistenţilor medicali, a responsabilităţilor şi munca în echipă. Sunt trecute în revistă domeniile de competenţă necesare, precum şi schimbările impuse domeniului educational. Aceste concept sunt illustrate de o cercetare cantitativă originală asupra educaţiei şi dezvoltării studenţilor de la specializarea de asistenţă medicală în context European, printr-un articol ISI rezultat al unui grant EU. Cercetarea demonstrează necesitatea dezvoltării unui model comun de mentorat necesar pentru o mai bună educa]ie practică a studenţilor asistenţilor medicali.

Al doilea capitol este dedicate nursingului comunitar şi sănătăţii publice şi conţine 5 articole ISI. În review sunt trecuţi în revistă factorii ce influenţează sănătatea (factori materiali, psihosociali, comportamentali şio financiari). În subcapitolul dedicate crizei este analizat modul în care banii influenţează sănătatea şi impactul crizei economice asupra sănătăţii populaţiei din România. Următoarele 3 subcapitole prezintă 3 articole ISI care au ca factor comun educaţia pentru sănătate a unor grupe de vârstă specific (bătrânii şi elevii şcolilor secundare din mediul rural) sau al unei patologii (diabetul zaharat).

Un alt obiectiv de interes pentru nursingul comunitar îl reprezintă sănătatea orală şi generală a populaţiei vârstnice rurale, subliniindu-se legătura dintre factorii socio-economici, aspectele educaţionale şi sănătatea oro-dentară şi generală a bătrânilor. Al treilea articol se referă la educaţia pentru sănătate şi promovarea aceteia în şcoli – un aspect important de nursing comunitar. A patra publicaţie studiază educaţia terapeutică a pacienţilor cu diabet zaharat, factorii ce îngreunează achiziţia cunoştinţeklor şi abilităţile de aplicare a

insulinoterapiei în practică. Al cincilea articol investighează markerii biologici în complicaţiile infecţioase acute ale diabetului zaharat, concluzionând că presepsina este asociată pozitiv şi este utilă ca predictor de mortalitate şi marker diagnostic al sepsisului.

Al treilea capitol include activitatea mea ştiinţifică în domeniul medicine interne, trecând în revistă mai multe studii clinice randomizate prin prisma expertului în patologia respiratorie, ilustrată prin 5 articole ISI ce revizuiesc strategiile terapeutice actuale în astmul bronşic, BPOC şi cancerul pulmonary cu celule non-small. Primele 2 subcapitole sunt dedicate terapiei biologice şi tiotropiului ca terapie adiţională în astm. Articolele următoare ilustrează eficacitatea terapiei triple fiuxe şi locul medicaţiei antiinflamatorii în BPOC. Ultimul articol revizuieste locul terapiei biologice în cancerul pulmonar cu cellule non-small.

A doua secţiune a tezei prezintă direcţiile viitoare de dezvoltare a carierei mele profesionale, academic şi de cercetare, incluzând activitatea cu studenţii şi rezidenţii care îşi desfăşoară stagiile în Clinica Medicală I.

Viitoarele direcţii de cercetare includ ca teme în domeniul nursingului stresul academic, rezilienţa şi sindromul de burn-out la studenţii de la medicină şi nursing pre- şi post-licenţă şi mentoratul ca posibilă soluţie, iar in domeniul medicinei interne aspectele ce privesc calitatea vieţii la pacienţii cu insuficienţă cardiacă.

A treia secţiune include cele mai relevante referinţe bibliografice folosite în redactarea tezei de abilitare şi include 442 titluri.

ABSTRACT

I am Associate Professor at the University of Medicine and Pharmacy "Grigore T Popa" from Iaşi. My experience as a physician is 34 years and as an academic teacher, 30 years.

I am a specialist in internal medicine from 1994 and consultant since 1998. I occupy the position of head of 1-st Medical Clinic in Emergency Hospital of "Saint Spiridon" since 2008. Between September 1990 and March 2001 I was an associated academic Professor's assistant for medical students in the IV-th and V-th study year in the English programme for internal medicine. Since January 2001 I occupied through contest the position of head of the 1-st Medical Clinic in Emergency Hospital of "Saint Spiridon" from Iaşi. In January 2002 I occupied through contest the position of Lecturer at the newly established discipline of Nursing, for the nursing specialization of the Medical Faculty in our University. In 2002 I sustained the contest for PhD degree in medicine with the thesis "Myocardial infarction of the right ventricle as an independent prognostic factor in acute inferior myocardial infarction", under the supervision of Professor Adrian Cosovanu in UMF Iasi. I am Associate Professor since 2003.

The present thesis, entitled "Facts and Challenges in Nursing and Internal Medicine", offers a global and synthetic overview of my scientific, professional and academic activity, in order to obtain the qualification to supervise PhD students. The presentation is structured in 3 sections, each divided into chapters.

The first section illustrates my scientific, professional and academic achievements and is structured in 3 chapters.

The introduction contains an overview of my development as a physician and an academic teacher and explains my dual research interest in internal medicine and nursing, giving a picture of the internationals grants I have been part of and the progress gained in my career.

The first chapter is dedicated to nursing, as a cornerstone in the continuum of health care. It contains a review on the place and importance of nursing in the actual context of demographic changes and challenges, which imply a change in the nurses' roles, professional accountability and team work. The domains of competencies required from nurses are reviewed as are the necessary changes in the field of nursing education. These concepts are further illustrated by an original quantitative research in nursing on the clinical education and training of nurse students in an European context, in an ISI article, as a result of an EU grant. The research concludes that the development of a nursing mentorship model in the former communist countries is required for a better practical education of nurses.

The second chapter refers to community nursing and public health and is contains the presentation of 5 ISI articles. In the review the factors which influence health are revisited, including material, psychosocial, behavioral and economic factors. It analyses the way money influence health and the impact that the economic crisis influenced the health of the Romanian population. The following 3 subchapters have in common the health education for specific age-related communities (elderlies and secondary school pupils) or pathology (diabetes mellitus).

Another point of interest of community nursing was the oral and general health status in an elderly rural population, emphasizing the link between socio-economic factors, educational aspects and the oral, dental and general health of the old adults. The third article refers to health education and health promotion in schools, as an important aspect of

community nursing. The fourth publication studied the therapeutic education in patients with diabetes mellitus, the factors that impend patients' knowledge and ability to implement insulin therapy in practice. The fifth article studied diagnostic markers in acute infectious complications of diabetes mellitus, concluding that presepsin is a positive and useful predictor of mortality rate and detector of sepsis.

The third chapter includes my scientific activity in internal medicine domain, reviewing expert opinions in respiratory pathology, illustrated by 5 ISI articles that review actual therapeutic strategies in asthma, COPD and non-small cell lung cancer.. The first two subchapters are dedicated to biologic and add-on therapies in severe asthma. It includes biologic therapy and thiotropium as an add-on treatment. The following articles illustrate the effectiveness of triple fixed inhaled therapies in chronic obstructive pulmonary disease and the place of anti-inflammatory therapy in COPD. The last one reviews the role of biologic therapy in non-small cell lung cancer.

The second section of the thesis describes the future guidelines for my professional, academic and research development, including students and residents that are following their study in the 1-st Medical Clinic.

My future research topics include academic stress and resilience and burn-out in pre- and post-registration nurse and medical students, as well as Mentorship seen as a possible solution to them, with its achievements and challenges.

The third section includes the most relevant references used in the preparation of this thesis and includes 442 titles.

SECTION I – SCIENTIFIC, PROFESSIONAL AND ACADEMIC ACHIEVEMENTS

1. INTRODUCTION

I have graduated the Faculty of Medicine of the University of Medicine and Pharmacy "Grigore T Popa" from Iaşi in 1986, with maximum grades, as a chief of promotion.

I have a clinical experience of 32 years near the bed side in the I-st Internal Medicine Ward and of 28 years of teaching medical and nurse students, in Romanian and English programme, at pre- and post-registration level. Ever since 1991 I had a double role, as a physician in training in internal medicine, after the national residency exam, and later, starting with 1994, as a specialist, as well as an external Professor's assistant involved in internal medicine and nursing teaching. This duality was and is very stimulating, giving me a wider overview of the two health profession and a solid insight in team working.

In 1994 I became a specialist in internal medicine in the l-st Internal Medicine Clinic of Emergency Clinical Hospital of "Saint Spiridon" from Iaşi and in 2001 consultant.

During 1999-2002 I prepared my Ph D Thesis on a cardiology subject: "Right ventricular infarction – an independent prognostic factor in the evolution of acute inferior myocardial infarction", under the supervision of Professor Andrian Cosovanu. The thesis was sustained in public on 28-th of February 2002. The thesis was highly original, using for the first time electrocardiographic morphometry in the analysis of the ischemic burden of acute inferior myocardial inferior and right ventricle infarction. I received my Ph D diploma on 29-th of July 2002 (Ministery of Education Order 4.198/2002).

In 2001 I became consultant in internal medicine, specialty that I practice to present, teaching in parallel medical students from the English language programme.

In 2001 the Faculty of Medicine started a new project, developing a second specialization for students: nursing. I was asked to take on the responsibility of building and developing the Nursing Discipline. After the contest for the Lecturer position I started a new and challenging path, which needed a deep insight into a different profession. I had to read a lot and understand the nursing process and the nursing diagnostics. In my didactic approach I wrote 4 books, dedicated to nurse students.

Two major events helped me in this quest: two European Projects, financed by the European Commission under the Erasmus Network umbrella.

The first one was TENN (Thematic European Network for Nursing) **Project EU No 102504-CP-2-2003-ERASMUS TN:** operating between 2002 and 2005. In this project there were involved 45 academic institutions, from 28 European countries. This project focused on three arias: leadership, mentorship and clinical supervision. My main interest was on mentorship, as a tool to empower students during their practice education. The gained experience enabled me to change the way I taught and supervised my nurse students. As a result of the experience gained in the project I published a book and delivered 2 oral presentations in the 5-th International Conference of FINE (acronym for International Federation of Nursing educators).

The second Project was Empowering the Professionalization of Nurses through Mentorship – EmpNURS (**510111-LLP-1-2010-1-FI-ERASMUS-ECUE**) financed by the European Commission between 2010 to 2013. This project involved universities and teaching hospitals from Finland, United Kingdom, The Czech Republic, the Netherlands, Hungary, Lithuania and Romania. We developed a pilot project for Mentorship, educating the mentors and the mentees and in the end writing a course to guide mentors, students and mentors' teachers' formation. This work resulted in 4 handbooks.

My academic career evolved in parallel and in 2005 I became Associate Professor through contest. I teach nurse students and residents in general medicine during their module of internal medicine.

From February 2008 I am also head of the l-st Internal Medicine Clinic in the Emergency Clinical Hospital of "Saint Spiridon".

During my teaching career I experienced a constant interest in the preparation of students and residents. One of the activities I enjoy best and am proud of is a one week scientific event: International Nursing Week. I started it in 2014 and developed it as a every 2 years event. This is a high quality manifestation, all lectures are presented in English and guests from European universities are invited. We received colleagues from the Netherlands, from Windesheim University of Applied Sciences, from University of Applied Sciences of Turku, Finland, from Kaunas Medical University in Lithuania, from Alicante University in Spain and Karol de Grote Catolishe Hogeschool from Belgium, and speakers from our university. In the last day of the week the lectures are sustained by our students. This is a very popular and stimulating event for students and teachers.

Starting with 2003 I had experienced stimulating and motivational Erasmus teacher exchange mobility in partner universities from Belgium, The Netherlands, Finland and Spain, during International Weeks or summer schools.

In 2012 the Faculty of Medicine introduced Palliative Care in medical and nurse students' curricula. I was again asked to prepare and develop the new discipline. In 2013, together with a colleague we published the first course for palliative nursing.

In the field of Palliative Care I took part in 2 European Projects:

Best Practice in End-of-Life-Care. A Challenge for Young European Nurses to implement best practices in End-of-Life-Care in Terminally Ill Oncology Patients (**2012/LLP/ERAMOB-IP/21**) financed by the European Commission (2013– 2014) – project that involved teachers and students from 7 countries.

Project **EU 2014-1-Ro01-KA203-002940**: Massive open on-line courses with videos for palliative clinical field and intercultural and multilingual medical communication - financed by the European Commission (2014– 2017). The project resulted in 7 books, in all the different languages of the participants.

Palliative care shares with nursing the holistic approach to the patients and the team work. Our interest in both disciplines is also illustrated in book chapters, offering an overview of palliative care in chronic, non-oncologic diseases, such as cardiovascular diseases.

As an internal medicine consultant my research interests also include respiratory medicine, cardiovascular, metabolic disease and immunologic diseases.

Nursing, and especially community nursing, shares interest area with public health and social issues.

The holistic approach is a constant element in my teaching and research activity. I consider that a physician should be a multidisciplinary researcher, an open minded teacher and a free spirit. I do my best to fulfill this quest.

CHAPTER 1 - NURSING IN THE CONTINUUM OF HEALTH CARE

1.1. STATE OF THE ART

Nursing is an art, a vocation, an autonomous health profession and a science, with evidence based practice. As the Nurses and Midwifes Council stated in 2010 the Royal College of Nurses in UK defined nursing as "the use of clinical judgment in the provision of care to enable people to maintain and recover health, to cope with health problems, and to achieve the best possible quality of life, whatever their disease or disability until death" (Royal College of Nurses, 2004).

The World Health Organization (WHO, 2003) stated that health care operates in congruence with the economic, political and cultural environment. Nurses represent the majority of the workforce in health care and offer care in a context shaped by these realities. Community nursing and public health are related domains.

Health, illness and disease

Health and bad health are influenced by a very diverse cluster of factors, such as life circumstances, social, economic, cultural, educational, spiritual, psychological and genetic. Nurses have to be aware of this and ready to react in a pragmatic manner to the growing need of people's interest to know more about their health.

There is a clear distinction between "illness" and "disease". Illness represents the patient's experience, while disease is a clinician's knowledge of a pathologic anomaly. Eisenberg pointed out this distinction in 1997:"Illnesses are experiences of changes in one's state of being and social function; diseases are abnormalities in the structure and function of the body organs and systems" (Eisenberg, 1997). In other words, the notion of illness encompasses the experiential aspects of sickness and social impact, it represents what the patient is living through.

Nurses are in an ideal position to deliver care. Nursing management and health promotion and therapeutic education are tightly linked. The objective of health promotion is to offer to the person knowledge and skills needed for healthy choices for their lifestyle. Every meeting with a nurse should provide an opportunity for teaching, not only the sick, but also the apparently healthy individuals.

Demographic challenges and changes

The population's ageing is a global problem and is a stringent challenge for health care delivery. As people grow old, their caring needs grow also, due to the association of chronic diseases, being frequently in a condition that needs hospital admission or long-term care in the community. It is estimated that 17% of people under 40 years have a chronic

condition, while for people older than 65, 3 out of 5 people have a chronic illness (Department of Health, 2008)..

The last decades have seen major technological progress in health care and medical advances. These changes come with ethical and economic challenges. The provision of growing complex care requires improved and new skills. The tendency to quickly discharge patients at home from hospital pinpoints the need of more sophisticated technical skills in community care and a better integration with social care. Patients have nowadays more knowledge about their disease and should take more responsibility for their self-management.

Nursing practice delivery is changing. There is need of more proactive interventions, both for current and preventive actions for individuals with chronic diseases. In 2008 the Department of Health in UK identified 6 domains of intervention: tackling obesity, reducing alcohol intake harms, decreasing addictions, reducing smoking rates, improving sexual and mental health (Vincent, 2003; Department of Health, 2008).

Policies for future health care emphasize the need to put the patient in the center of care, the focus being on constantly improving health's outcomes and encourage clinicians to become more creative. People are now expecting not only quality health services when they need them, but also service them can manage and shape themselves. Nurses are in a privileged position to satisfy these needs and challenging demands

Changing Nurses Roles

The profession of nursing is growing in complexity, role, skills and accountability. In Western European countries and in the United States there are nurse consultants, nurse practitioners and advanced nurse practitioners that practice skills previously restricted to physicians' roles.

There are clinics led by nurses and there are nurses with independent prescribing competences, allowed legally.

Nurses have more and more complex roles nowadays (Nursing and Midwifery Council, 2008), such as:

- organizing the care focusing on patient's needs;
- ensure that the patient will have a pleasant experience with nursing care and will receive quality services;
- work in the continuum of care, from hospital to community and be able to use telemedicine;
- have the required skills and competencies to work with the elderly patients, with chronic diseases or long-term conditions, with physical and mental health problems;
- deliver preventive and health promotion interventions;
- perform advanced technical skills;
- work in different and diverse employers or practice independently where fit;
- work in multidisciplinary teams, as leaders in and out of hospital settings, across health and social services in the community;
- work with diverse types of practitioners;
- deliver quality care and offer best value for money.

Professional accountability

The work and responsibility of registered nurses is guided by the professional's organization code of ethics and practice. This document establishes the standards of conduct for nurses and midwifes. This code stipulates that when a nurse is delegating a task to an auxiliary health worker she or he remains accountable for the appropriateness of the delegation. It is important to ensure that those to whom they delegate the task are apt to perform safely and well the instructions, confirm that the results of the task satisfy the quality standards and ensure that the persons to whom they delegate are supported and supervised.

In the last two decades nursing education changed from diploma level to bachelor's degree and nowadays in most EU countries and in the United States is done in universities. In future diploma level programmes will no longer be available for nurses, there will be only degree programmes.

The degree nurses would practice more independent and innovative, being able to demonstrate higher levels of professional judgment and decision-making in a complex care environment; provide evidence-based care safely and meeting the quality standards; be members and leaders of multidisciplinary teams of health workers educated at bachelor's level and provide leadership in empowering their peers and promote change in the development of clinical practice (Nursing and Midwifery Council, 2008).

Team work

Team work is a key factor for quality of care, both in theory and in practice. Partnership should include not only other medical or social health care professionals, but also include the patients and their families. Patients' voices will become even more important in the way care is delivered and evaluated. This team work means that nurses from hospital and community will have to develop new ways of practice together with colleagues from social services, public health in diverse environmental settings and different clinical scenarios. This requires firm and good clinical governance and leadership. Clinical judgment, decision-making skills and safe practice will ensure a leading position for nurses in the multidisciplinary team. Leadership, management and team work represent one of the 4 important domains of competencies necessary for nursing practice (Nursing and Midwifery Council, 2008).

Domains of competences required from nurses

a. Professional values

All nurses have to offer care and safeguard people. They have to practice autonomously, be responsible and accountable for their work. They should offer safe, quality and compassionate patient-centered care and evidence-based practice. Their interventions should demonstrate respect, recognize dignity and human rights of their patients. They must work together with other health and social care providers, with the patients and their families in all environments, in the community, taking a shared decision (Nursing and Midwifery Council, 2008).

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b. Communication and interpersonal skills

All nurses should prove proficient communication and good interpersonal skills. Communication should be effective, clear, safe, compassionate and respectful. They should use all means for communication, including various communication technologies and telemedicine. When in charge with a person with disabilities, nurses should strive to work with service users and others to obtain the needed data to attain and promote optimum health and ensure equitable access to care and health and social services (Nursing and Midwifery Council, 2008).

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c. Nursing practice and decision-making

All nurses should practice and promote health and wellbeing for their patients, practicing safely, autonomously, compassionately, safely and knowledgeable.

They should evaluate all somatic, physical and mental health needs of persons of different ages and health conditions that come into their care.

They must be able to offer effective and immediate care prior to referring to a specialist, no matter their area of practice.

They must meet complex and coexisting needs in their own practice domain, in different settings, such as hospitals, community or people's home.

All services should be based on the best evidence available and comply with national guidelines.

Decision-making should be shared with other health care providers from the multidisciplinary team, the patient and the family members. The latest should be informed of the wide range of possible interventions, in order to obtain their informed consent. All nurses should understand how the determinants of health (behavioral, social, economic and cultural factors) influence health, illness and interfere with the planning and delivery of care(Nursing and Midwifery Council, 2008).

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d. Leadership, management and team working

All nurses should be professionally accountable for their practice and provide clinical safe care in order to improve and provide good nursing services, and constantly respect the standards of care. They have to be able to efficiently respond to challenging situation, practicing autonomously and confidently, managing others and themselves efficiently and safely. They must seek and develop opportunities to improve care. They have to prove the potential to acquire further leadership and management skills during their perceptorship period and ever after (Nursing and Midwifery Council, 2008).

Changes to nursing education

At the end of 1990's, European Ministers of Education agreed in Bologna to construct European wide development reforms in all fields of education, including health care education. This process led to several reforms which have explored development phases of education systems in European countries and tried to define the main structure of professional education (Suhonen et al., 2009; Salminen et al., 2009).

During the last decade many of the current European Union (EU) countries, from the former Communist Block (the Soviet Republics' Union and aligned countries) in particular,

have undergone substantial re-organization of nursing education that also aimed at the transition of registered general nurse (RGN) training programs from vocational or hospital-based school systems to Higher Educational Institutes (HEIs universities or colleges). The survey of the training of nurses in the EU certified the fact that in 2012 sixteen EU Member States educated general care nurses exclusively at university level (Bachelors' degree) and two Member States had both academic and diploma level education for nurse students in vocational colleges (DG Internal Market, 2012).

It is emphasized that higher education of nurses is a particular phenomenon in the former Soviet Union and aligned countries and it is not further associated only with getting clinical knowledge and skills, but also with the need for the development of professional identity and values, the acquisition of scientific knowledge and the search for its application when implementing the benefits of modern nursing education, humanistic ideas and professional autonomy (Karosas and Riklikiene, 2008).Increasing globalization has extended to nursing education programs even more as students move from country to country seeking international opportunities and entire programs are being delivered abroad. Internationally moving students, the expansion of health care service across borders and a highly mobile nursing workforce altogether demand an examination of how we educate nurses for their profession. Numerous national, regional and international research initiatives have focused specifically on the education of nurses and recognize the importance of ensuring not only a sufficient quantity, but also the quality and relevance of health professionals joining the workforce, preparing socially accountable professionals, able to practice collaboratively and to deliver care in current complex and global international context of practice (Barry, 2012; Tichelaar et al., 2012).

Together with modern nursing theories, clinical training in a real health care environment has always been in the center of nursing education supporting students' transition from the “didactic classroom environment to the hands-on clinical world” (Zipp and Colber, 2014).

Clinical education experiences support the mastery of psychomotor, cognitive, and affective behaviors needed for competent entry-level practice. Despite the fact that formal mentors in nursing education in the countries under consideration (the Czech Republic, Hungary, Lithuania and Romania) is just a recent practical implication, there is a wide range of international evidence regarding the effective nursing theory and practice integration with changing health care needs and the improvement of educational, psychological and managerial competencies of practicing nurses through mentorship relations (Warne et al., 2010; Tichelaar et al., 2012).

The nursing program providers usually raise the similar questions seeking the improvement and quality assurance of clinical training of student nurses: What are the main features of a good clinical learning environment? What is an ideal duration of a clinical training placement? What kind of mentor-student relationship has to be developed during clinical training? What are the most important elements of good co-operation between HEIs and a health care service organization? There is still a limited number of studies considering these questions in an international context (Suhonen et al., 2009).

The existent situation of clinical teaching and students' satisfaction with the learning environment has been explored in four relatively new member states of EU: the Czech

Republic, Hungary, Lithuania and Romania inside the EmpNURS Project (www.empnurs.eu), during the preliminary exploratory phase, and this article describes the results of the exploration. The analysis of the quality and the relevance of clinical training as a substantial part of the nursing programme from students' perspective are important to ensure the acquisition of expected competencies of graduating nurses and strengthen educational systems further by sharing good practices within the EU countries. Finally, evaluation of how we educate future nurses is essential if nursing is to lead the world to better health (Barry, 2012; WHO, 2013).

In 2000 a major change in nurses' education happened in our country, with the development of academic education in universities of medicine and polytechnics. However our society is not yet ready to give up the diploma only level for nurses and that is a pity, because we can't compare with the western EU countries because of this.

Degree-level education offers more competencies for their bachelor nurses, as a promise of a better quality care, patient-centered and evidence-based.

Degree level nurses should:

- Practice more autonomously and independent, in an innovative way, based on a sound professional judgment in a complex care environment;
- Provide effective, safe and evidence-based care, wisely managing the economic and material resources and offer continuous care from hospital to community settings;
- Act as members and frequently leaders of multidisciplinary teams;
- Provide leadership and empowerment towards change and develop quality services.

My personal involvement in nurse students' education and nursing care begun in 2001, when the Nursing Discipline was created for the Nurse students' specialization inside the Faculty of Medicine in our University.

Therefore my interest and preoccupation in this domain are illustrated by the following grants and articles, as follows:

Grants:

- TENN (Thematic European Network for Nursing) Project EU No 102504-CP-2-2003-ERASMUS TN: 2002 - 2005.

- Empowering the Professionalization of Nurses through Mentorship – EmpNURS (510111-LLP-1-2010-1-FI-ERASMUS-ECUE) financed by the European Commission between 2010 to 2013. This project involved universities and teaching hospitals from Finland, United Kindgom, The Czech Republic, the Netherlands, Hungary, Lithuania and Romania. We developed a pilot project for Mentorship, educating the mentors and the mentees and in the end writing a course to guide mentors, students and mentors' teachers' formation. This work resulted in 4 handbooks.

Articles:

- **ANTOHE I,** Riklikiene O, Tichelaar E, Saarikoski M. Clinical education and training of student nurses in four moderately new European Union countries: Assessment of students' satisfaction with the learning environment. Nurse Education in Practice, 2016; 17: 139-144. http://dx.doi.org/10.1016/j.nepr.2015.12.005

1.2. QUANTITATIVE RESEARCH IN NURSING

1.2.1. INTRODUCTION

My interest in Mentorship developed starting with 2003, when I was part of the TENN Project (Thematic European Nursing Network) and became stronger after the EmpNURS Project (Empowering the Professionalization of Nurses Through Mentorship) during 2010 to 2013.

Empowering the Professionalization of Nurses through Mentorship 510111-LLP-1-2010-1-FI-ERASMUS-ECUE (acronym **EmpNURS**) was a research and development Programme operating for 3 years (2010-2013) under the Erasmus umbrella, financed by the European Union Commission. It had a total budget of 367302 Euro, 75% provided by the EU Commission – 275270 Euros, the rest of 25% being financed by each participant institution.

The project was designed for registered nurses, nurse students and academic teachers educating them.

The EmpNURS consortium consisted in 11 institutions – 7 Higher Academic Institutions and 4 teaching hospitals from the Czech Republic, Lithuania, Hungary, Romania, the Netherlands, the United Kingdom of Great Britain and Finland. The partners were:University of Applied Sciences, Turku, Finland (Coordinator Institution), Masaryk University, Brno, Czech Republic, Teaching Hospital Brno Bohunice, Czech Republic, Institute for Basing and Continuing Education of Health Workers, Budapest, Hungary, National Institute for Rehabilitation, Budapest, Hungary, Kaunas University of Medicine, Lithuania, Second Kaunas Clinical Hospital, Lithuania, Windesheim University of Applied Sciences, Netherlands, University Emergency Hospital "Saint Spiridon", Iasi, Romania
University of Medicine and Pharmacy "Grigore T Popa" Iasi, Romania, University of Salford, United Kingdom

In the first year of the project the partners explored the content of students' supervision and mentorship in the participating countries, in order to reach a common ground of understanding.

Nursing, as a profession, varies greatly across Europe. Partly this is a consequence of significant differences in the way nurses are educated. Learning to become a nurse is a multidimensional process that requires significant time spent with patients as well as understanding nursing theory. A crucial factor within all nurse education systems should be the relationship between the mentor and student. Such mentorship relationships are best

illustrated in the way qualified nurses promote learning opportunities for student nurses during placements in clinical practice. However, such approaches are not universal. Nurses are not always taught by other nurses in practice, and some qualified nurses don't view such activity as their responsibility. The processes of harmonization within European nursing educational systems seek to address such incongruence, and in so doing, promote an empowered and better educated nursing profession.

We compared the way nursing students' clinical practice is delivered in the participating countries and systematically explore the literature in order to define the international context of clinical supervision for students and mentorship. The results of this exploration were presented above.

The EmpNURS project aimed at benefiting nurse educationalists and student and qualified nurses. Building on previous work, mentorship training courses were facilitated in four relatively new member states within the EU (the Czech Republic, Lithuania, Hungary and Romania).

The main aim of the EmpNURS Project was to develop mentors for the clinical placements of the nurse students. Each mentorship course was specifically geared to the cultural, professional and organizational needs of the participating partners. The Mentorship course addressed to mentors, faculty teachers and students and was piloted in the 4 former communist countries, in the partner universities from.

In the dissemination phase of the project the mentors' course was implemented in the partner universities from the Czech Republic, Lithuania, Hungary and Romania.

The project outcomes were:

- Improved supervision skills of qualified nurses;
- A homogeneous range of Mentorship models;
- Enhanced integration of education and practice organizations;
- Improved harmonization of approaches to European nurse education.

Nursing is a clinical based profession; therefore **the learning environment** is crucial for nursing education experience (Warne, 2010; Holland, 2012).

As the changes in the clinical care and therapy of patients changed in the last 2 decades, education of healthcare workers also changed, trying to cope up with the former (Launders, 2000; McBrien, 2006; Saarikoski, 2018). The clinical learning environment is challenged, because often it is ill-defined and not predictable (Williamson, 2001), due to the complex clinical conditions of the patients and their evolution. So, new strategies regarding timing, topics to teach in practice and students' assessment have to be put in place in order that learning in practice setting takes place. Mentors and teachers from the universities have to find these new strategies to promote an efficient clinical learning environment (McBrien, 2006).

The clinical learning environment has been seen as a support for development of clinical skills, a way to shift theory into practice, while sustaining students in their professionalization in nursing (Burns 2005; McBrien, 2006). McKenna and Wellard (2003) describe the clinical learning environment as a mechanism that expands the theoretical classes in school into the nursing practice environment. So, as the school gives theoretical

knowledge to students, the clinical practice allows the formation of competent practitioners (McBrien, 2006).

Nursing students' learning occurs best in practice, the workplace allowing the development of essential professional skills (McBrien, 2006). Delivering a questionnaire to nursing students in their terminal year of education, Parker (1996) found that students valued more the clinical settings, in term of relevance, intellectual challenge, teaching methods and decision-making than the school taught lessons. In this study, 90% of students favored learning in practice, saying that learning only occurs when theory and practice meet.

This is why one can say that the quality of the clinical learning environment is the most important determinant of students' learning process. In practice, students have to adapt from an environment that encourages thinking in an environment that puts accent on doing (Napthine, 2006; McBrien, 2006). The stress related to this transition, from the university to the clinical workplace can be disturbing for students and their learning process (Lofmark, 2001; Dolan, 2003). A friendly clinical environment and the support of nursing staff can create a safe medium for the students, encouraging the students and allowing them to attain their maximal potential for learning (Donal, 2003). In 2001 McAllister demonstrated in his study that a positive relationship with the mentor, acceptation and feeling of belonging to the care team were essential to construct a good learning environment. The attitude of the staff is crucial in determining the socialization of students in the clinical setting, helping them to acquire their new role (McBrien, 2006).The reverse: negative attitudes, rejection and neglect of the nursing students on the ward reduce the learning opportunities for students, lowers their self-esteem and, in the end, negatively impact the delivery of care (McBrien, 2006).

Due to the increased difficulty of patients' care, with multiple comorbidities and the shortage of staff some nurses on the ward perceive students as a supplementary burden on their work and are reluctant in encouraging students to perform advanced tasks, limiting their interventions to basic care (Beeman, 2001; McBrien, 2006).

The clinical learning environment is complex, including a multidimensional network of social relationship (Hooven, 2014). These aspects include psychosocial elements resulting from the interaction of the staff with the workplace, the management culture in the community and the nature of care in the ward (Saarikoski, 2018). The quality of the collaboration between the University and the clinical placements imprint the quality of the clinical learning environment (Saarikoski, 2002).

- The psychosocial climate of the nursing staff on the ward

The group dynamics and the psychosocial laws on the ward are similar to those in any work community. When there are no disrupting and obstructive factors, the work group can implement its fundamental role. This favorable atmosphere will be also felt and adopted by the students. The learning in such a placement will be a good experience for the students. In a non-favorable environment the students will concentrate on maintaining their personal psychosocial safety (Saarikoski, 1999; Pinto, 2010).

The atmosphere on the ward depends on the management style of the place. The ward manager can have a direct or indirect role in students' supervision, through the clinical climate providing good or poor conditions for learning to occur (Saarikoski, 2018). In units highly oriented to students' learning there are good communication skills and students are

encouraged to ask questions and discuss their learning goals with the staff. The students are seen primarily as learners, not workers (Saarikoski, 2002).

- The quality of care and students' learning experience

The fundamental element that determines the results of nursing students' learning experience is the quality of care delivered by the ward. It is also important that the students can attend and participate in the continuum of care, so they can understand what is happening with the patient and have an integrated and comprehensive view on the patient's status (Warne, 2010). Holistic care and documentation offer a realistic view on the requirements of the nursing profession (Saarikoski, 2018).

The contact with the patients promotes integration of theory into practice and provides a good learning opportunity to students, illustrating that the nurse has to care not only on the client's physical needs, but also the psycho-social status of the patient. The same factors influence the relationship between the students and their mentors (Andersson, 2015).

- The development of the professional identity

The development of the professional identity is a continuous process, which starts during the students' first years of academic education, in school and in the clinical setting. This is a process that implies a professional socialization, during which the students assumes gradually the values, attitudes, knowledge, skills and moral concepts already existing in the nursing profession. The role model of the student's mentor is very important for the professional socialization (Donaldson, 2005; Larson, 2013). Professional identity is the result of combining the personal and the professional self of the care worker (Johanson, 2012; Larson, 2013; Saarikoski, 2018).

The mentorship model described above is common for the West European countries and in the Anglo-Saxon world. However this situation is not universal. There are countries in which such mentorship model is unknown, or the used supervision model is different and there are countries in which nurses don't engage at all in students' clinical learning (Saarikoski, 2007; Warne T, 2010, Antohe, 2016).

In the European Project EmpNURS (Empowering the professionalization of nurses through mentorship), which ran during 2010 to 2013, in the exploration phase of the project, we conducted a study on how nursing students clinical placements were organized and achieved in four moderately new European Union countries (the Czech Republic, Hungary, Lithuania and Romania - Antohe, 2016). Data were electronically collected, using the CLES questionnaire. Our article explored the satisfaction of nurse students with the learning environment and, moreover, with clinical placement education of student nurses in four EU countries. The results highlight the individualized supervision model as a crucial factor of students' total satisfaction during their clinical training periods.

1.2.2. MATERIAL AND METHODS

Study setting and sample

The sample (N ¼ 418) was drawn from student nurses in four HEI's located in the Czech Republic, Hungary, Lithuania and Romania during the exploratory phase of the EmpNURS Project (510111-LLP-1-2010-1-FI-ERASMUS-ECUE) in the spring of 2011

(www.empnurs.eu). The students had just had a clinical placement as a part of their studies for registered nurse (Bachelors' degree).

Study design and instrument

The quantitative study design was applied for this study. The survey method was selected using a questionnaire including 43 items. The questionnaire utilized a part (25 items) of a validated research instrument: the Clinical Learning Environment, Supervision and Nurse Teacher (CLES þ T) scale (Saarikoski et al., 2008). These 25 items evaluate four domains: the Educational atmosphere on the ward (8 items), the Leadership style of the ward manager (4 items), the nursing care in the ward (4 items) and the content of the supervisory relationship (8 items). The respondents evaluated all items of the questionnaire using 5 points Likert scale. For instrument reliability we measured Cronbach's alpha values of the instrument sub-dimensions. They varied from 0.85 to 0.95 and proved sufficient high internal consistency of the scale. Additionally, the questionnaire included 18 background variables connecting demographic factors and structural elements of the clinical placements. The questionnaire was translated into the four target languages of the survey countries using double-blind translation procedure (Bechling and Law, 2000).

Data collection and analysis

Data collection utilized a web-based questionnaire. The link to the questionnaire was submitted to students via e-mail and this email message acted as an informing letter about the study. The students gave their informed consent to participate in the study as they answered the questionnaire. Data confidentiality was guaranteed by the anonymous character of the answers. The collected data were analyzed using descriptive statistics and cross-tabulation. Chi-square was used to test the connections between students' experience with clinical learning environment and related factors; $p < 0.05$ was considered significant. Comparisons between the four countries, using statistical tests, were not operated because of the small number of sub-samples. Therefore some values describing sub-samples are presented in this paper, without checking their statistical significance. All analysis was operated with SPSS 18.0 software.

1.2.3. RESULTS

The study sample included 418 nurse students studying for a registered general nurse Bachelors' degree. The clinical instruction hours comprised at least 50% of undergraduate level nursing program duration. Most of the students were younger than 25 (75% of study sample), while 25% were older than 25 and being 88 percentile female. The respondents were mainly students in their first year (42%) or second year (29%) of their nursing education.

Student sample is depicted in Figure 1. The socio-demographic structure of the sample is depicted in Figure 2.

One can see that in all four countries students younger than 25 years were the most. The female gender was significantly more represented among students in all four countries.

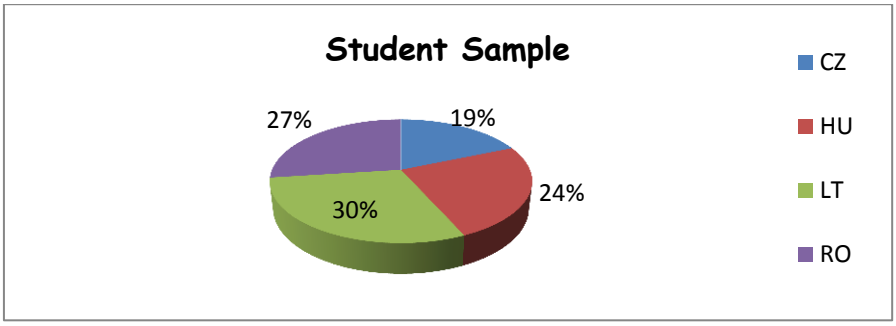

Figure 1.1. The structure of student sample

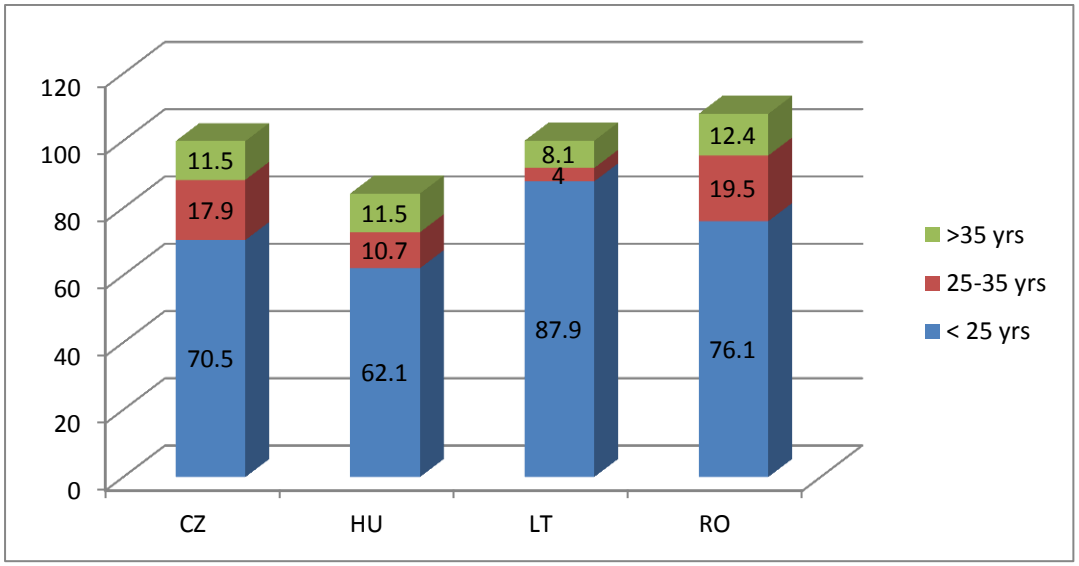

Figure 1. 2 The distribution of student samples in age groups

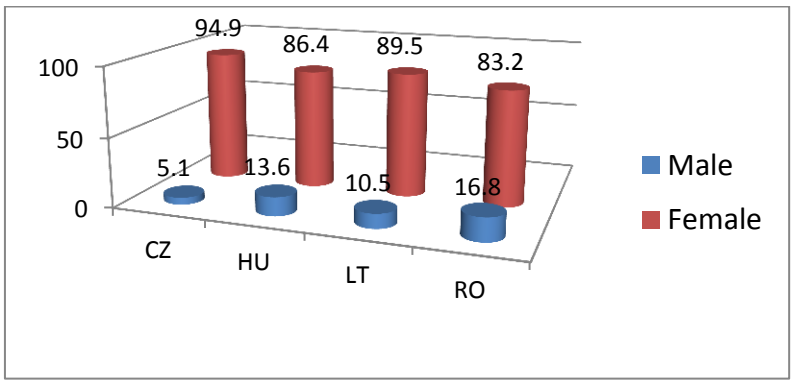

Figure 1.3 The distribution of student samples regarding gender

Organization of the clinical placements

Half of the student nurses had short term placements (1-6 weeks) and the other half experienced long term (7 weeks or more) clinical placements. Over 40-week-long placements were typical in Hungarian and Romanian sub-samples and the mean of placement duration in the whole sample was 10 weeks. Theoretical lectures were also delivered during the clinical placements in 47% of the study sample. Theory studying days during the placements accumulated on students who had long-lasting placements (7 weeks or more). Clinical placements were organized mostly in the hospital and only in 5% cases in the community. Most of the hospital wards receiving students were medical (36.6%), surgical (15.6%) or pediatric (12.2%) wards. The rest of the practice placements were gynecology and obstetrics (6%), geriatric ward (6%), psychiatric hospital (1.6%) and 22% were miscellaneous (community care and GP's office, palliative care and terminal care settings).

The organization of clinical practice is presented in Table 1.1 and depicted in Figure 1.4.

Table 1.1 – The sub-samples by country, basic features of general nurse (degree) education and organization of clinical practice (N=418)

	Responsible operative organization of education	**Duration of the total course**	**% ratio of clinical practice**	**Duration of the placement**		
				Mean	**Minimum**	**Maximum**
The Czech Republic (Brno) N=78	University college since 1990, early secondary schools	3 years	50%	10 weeks	1 week	14 weeks
Hungary (Budapest) n-103	University college since 1990, early secondary schools	4 years	50%	14 weeks	1 week	46 weeks
Lithuania (Kaunas) N=104	University college since 1990, early secondary schools	4 years in University and 3,5 years in College	50%	5 weeks	2 weeks	12 weeks
Romania (Iasi) N=113	University college since 1990, early secondary schools	4 years	50%	11 weeks	1 week	45 weeks

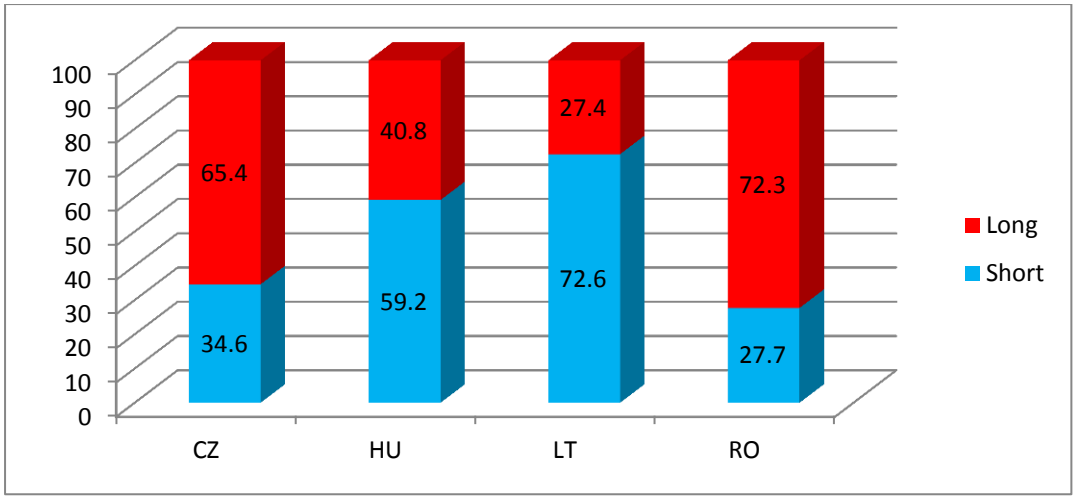

Figure 1.4 – Distribution of clinical settings regarding duration of the placements

The organization of the clinical placements in respect of the specialty of the wards is represented in Figure 1.5.

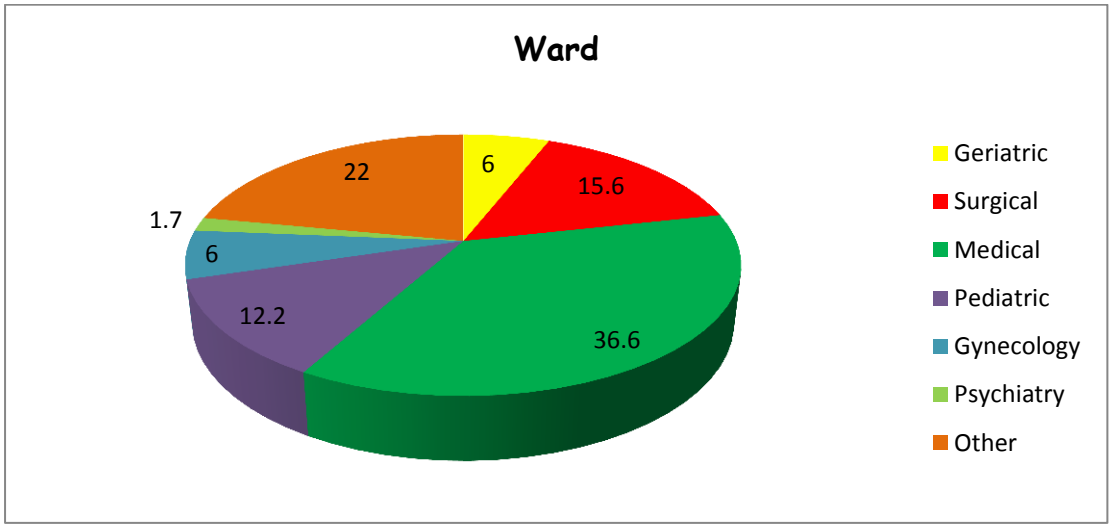

Figure 1.5 – Distribution of clinical placements on specialties of the ward

Most students were placed on medical wards, surgical units or pediatric wards.

Students' evaluations of their clinical learning environment

Students evaluated the learning environment in four domains using 25 items of the CLES scale. The total mean of the CLES scale was 3.87 in 1 to 5 continuum scale. The students were mainly very satisfied for their placement and they evaluated with high scores also the CLES scale's items describing their learning environment and experiences in their supervisory relationship (Table 1.2).

Table 1.2 . The sub-samples by country, basic features of general nurse (degree) education and organization of clinical practice (N=418)

Sum-variables and eight examples of the items	**Mean (1-5 scale)**	**Std. deviation**	**αValue**
Sum-variable 1: Educational atmosphere on the ward (9items) (The highest and lower scored items of the sum-variable:	3.74	0.88	0.90
The staff was easy to approach	4.12	1.04	
There were sufficient meaningful learning situations on the unit	3.39	1.47	
Sum-variable 2: Leadership style of the ward manager (WM) (4 items):	3.85	0.91	0.87
The WM regarded the staff as her/his ward as a key resource	3.94	0.94	
Feedback from the WM could easily considered as a learning situation	3.74	1.12	
Sum-variable 3: Nursing care on the unit (4 items):	3.99	0.85	0.85
The unit's nursing philosophy was clearly defined	3.81	1.05	
Documentation of nursing was clear	4.16	0.95	
Sum-variable 4: The content of the supervisory relationship (8 items):	3.91	0.99	0.95
My supervisor showed a positive attitude towards supervision	4.23	0.99	0.95
I felt that I received individual supervision	3.64	1.23	

Models of supervision provided by clinical staff

Most typical supervision model in our sample was group supervision (56%). A quarter of the sample had had an individualized supervisory relationship. A small part of students' sample (11%) did not have any supervision by the unit (Table 3).

The commonest professional background of the supervisor was in nursing (63%). A remarkable part of students (19%) had had physicians as supervisors, mostly in Romania (55%). The rest of the students (18%) had a supervisor from the university or some other person from the unit, in most cases in Hungary. Group supervision model was the commonest in Romanian sub-sample, where 83% of the students were supervised in a group and model of individualized supervision was most common in Lithuanian sub-sample, where 41% of the students were supervised by one-to-one relationship by the ward staff. The background of the supervisors is depicted in Figure 1.6.

The students' utter satisfaction towards their learning experience

Students' utter satisfaction was estimated using 3 items: "Can the unit be seen as a good learning environment?", "Are you satisfied with the supervision you have received?" and "How satisfied were you with the clinical placement as whole?" The students' utter satisfaction was considered with crucial background variables (gender, age, studying year, clinical specialty, placement duration), but none of these items significantly related with the students' utter satisfaction (p value of Chi-test >0.05).

The first clear connection was found with the supervisory model of clinical practice. The most satisfied students were those with an individualized supervisory relationship (mean 4.13), and most dissatisfied students were students without any supervision (mean 2.89) (Table 1.3). The second factor that was linked with total students' satisfaction was the professional background of supervisor. The most satisfied students were those who have had

nursing based supervisors (mean 4.05), and most dissatisfied students were those without any supervision (mean 2.89). The students' own motivation for the placement and clinical learning was mainly very high (mean 4.1). Statistically, the students' own motivation was significantly related with their utter satisfaction of clinical placement (p-value of Chi-test < 0.001).

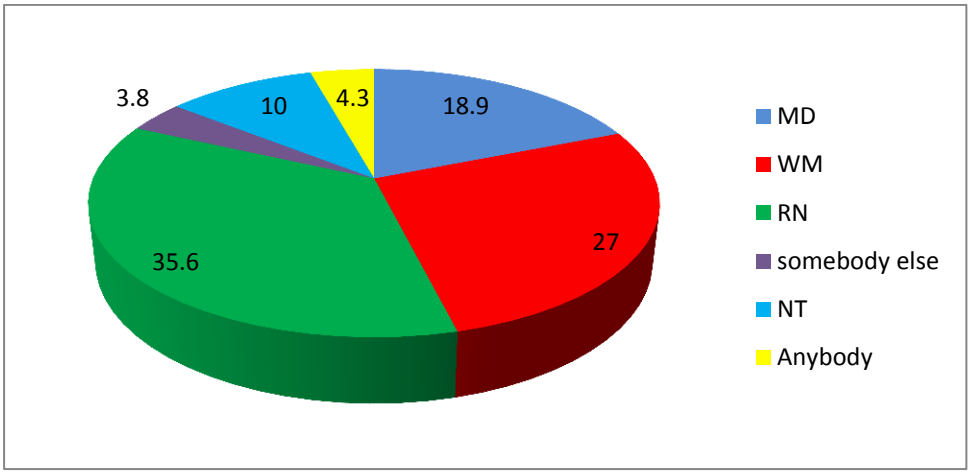

Figure 1.6. The background of the supervisor

Table 1.3. Connection between nurse teacher meeting frequency and usage of communication tools

	No meeting	**Meeting with the nurse teacher**		
		1-3 times	**More often**	**Total**
Usage of e-Communication tools	97 88%	70 55%	82 45%	249 60%
1-3 times	12 11%	50 40%	62 34%	124 30%
4 times or more often	1 1%	6 5%	37 21%	44 10%
Total	110 100%	128 100%	181 100%	417 100%

Communication with the course teacher

Over half (51%) of our student sample had met their nursing teachers from the Higher education institution (HEI) at least 3 times during their clinical placements, but 26% of the students had not had such connection at all. Less than half of our students' sample (40%) had used e-communication (e-mail, text messages etc) with their nurse teacher. This kind of virtual e-communication applied to students who had also had 'face-to-face' contacts with their course teacher.

Students' professional identification during the placements

There were two different questions related to the professional identity: "How important is it to you that the professional background of your supervisor should be in

nursing?" and "Who was the most important person to help you better understand the core concepts of the nursing process?"

The professional background of the mentors in our sample was mainly as registered nurse or ward manager, but one could also encounter physicians and nurse teachers from the nursing HEI as supervisors. Eighty percent of students in our sample reported that nursing background of supervisor is very important. A minority (5%) thought that this is not at all important and 15% considered that it has only minor significance. In 36% of cases students in our sample considered that teachers in HEIs and supervisors were equally important in explaining the core concepts of the nursing process; 35% of students considered the supervisor's role more important, and 26% favored HEIs teachers' role in this process.

1.2.*4.* DISCUTIONS

The concept of mentor

The concept of **mentor** goes back to the Greek mythology, when Mentor, a friend of Odyseus was asked by the king to take care of his son Telemachus, teaching and guiding him while he was away, fighting in the Trojan war (Caroll, 2004; Pellatt, 2006).

From a historical perspective, the first nurse mentor was Florence Nightingale. In 2003 Lorentzon and Brown's study of her correspondence showed a mentorship relationship between her and Rachel Williams, matron of St Mary's Hospital, Paddington.

In 1979 Atwood described a pilot project in a St Mary's children's hospital introducing mentors for nurse students in Saint Francisco. The mentors were seen as role models, the students progressed more quickly and the care became better.

In 1984 Darling identified three basic roles for the mentor: inspirer, investor and supporter. The author also described multiple characteristics of a mentor, such as: model, envisioner, energizer, investor, supporter, teacher–coach, feedback-giver, eye-opener, door-opener, idea-bouncer, problem-solver, career-counselor and challenger.

The mentor's role is seen as a short time relationship, during the nurse student's practice (Bennett, 2003). The mentor is seen as the professional practitioner who supervises, facilitates learning and assesses nurse students in the clinical settings.

The British Nurse and Midwifery Council (NMC) identified in 2004 eight mandatory standards for mentorship and mentors. In order to achieve these standards the mentors support the nurse students, applying theory into practice, give constructive feed-back and encourage students' reflection on it.

The standards for mentorship and mentors identified by NMC are the following:

Communication and an effective working relationship

- Assist students to integrate into practice settings
- Provide ongoing support for students

Facilitate learning

- Identify current learning needs
- Assist students to integrate theory and practice
- Create and develop opportunities for students to identify and undertake experiences to meet their learning needs

Assess students using approved procedures
Act as a role model:
- Demonstrate effective relationships with patients and clients
- Develop an environment of good practice
- Assess and manage clinical developments

Create an effective learning environment
- Undertake quality assurance and quality audit

Improve practice by initiating and supporting change
Identify, apply and disseminate research findings
Contribute to course development and/or review

Mentors have to be willing to adopt a flexible approach towards students, based on students' needs and previous learning experience, in order to achieve an effective learning (Warren D, 2010).

A good mentor is seen as a role model, an effective teacher, an approachable person, enthusiastic, enabling and facilitating the students to practice skills learned under supervision and gradually reducing the supervision as the student progresses (Atwood, 1979; Ferguson, 2007; Gray, 2007; Waren, 2010; Gray, 2006; Carr, 2008; Royal college of Nurses, 2009; Ekebergh, 2011).

Being a mentor is an essential role nurses experience in clinical practice, offering a safe and positive learning environment, while coaching, teaching and facilitating students' learning in order to become good nurses (Kneafsay., 2007; Ali, 2008; McVeigh, 2009; Leyshon, 2010; Holland, 2013).

Mentors need solid knowledge and skills in order to implement their supervising, guiding and assessing roles and develop the learning environment for students (Burns, 2005; Pellat, 2009; Tichelaar et al, 2013).

The mentor is the key person in the clinical setting that supports and helps nursing students to gain skills and become competent and knowledgeable professionals (Holland, 2012). Problem based learning in clinical practice under the supervision of the mentor proved very efficient (Jowett, 2007; Aari, 2008).

The nursing student as a mentee

The mentee is someone who learns under the supervision of a mentor, receiving guidance and support to learn in a clinical setting (Tichelaar et al., 2012).

The relationship between the mentee and the mentor is a key factor in determining the quality of the learning experience (Casey DC, 2011). A successful teaching style for the adult learner should aim to motivate and facilitate rather than dictate, due to the learner's own existing experience and previously formed learning style (McBrien, 2006; Gidman, 2011). Mentors should be willing to adopt a flexible teaching approach according to the needs of their student, in order to ensure effective learning (Middleton, 2009; Warren, 2010; Daylan, 2012).

In a 2000 research (Watson, 2000) students emphasized the importance of having a good role model in clinical areas to acquire good practice (Papastravou, 2010). This can be

problematic sometimes due to the shortage of mentors or other qualified staff. Watson (2000) found that students, mentors and lecturers pinpointed the importance of having a role model involved in practice teaching. Learning in practice should encompass areas such as showing the mentees practical skills, explaining what they did, relating theory to practice and giving the students the opportunity to practice what they have been shown (Donaldson, 2005; Royal College of Nursing, 2006). Caring behaviors can be learned from mentors, while acquired negative attitudes are difficult to change (Donaldson, 2005; Kneafsay, 2007).

It is the responsibility of the mentors to correctly assess students and identify negative attitudes and behaviors and fail those students who do not meet clinical performance standards (Jervis, 2011).

Sometimes, due to the oversized number or nursing students and mentors shortage in the clinical setting, a more experienced student can act as a peer mentor for the newcomer student (Gilmour, 2007). It is also possible to encounter a team of professionals acting together as mentors for nursing students, achieving in fact an inter-professional mentoring (Chapple, 2004; Barton, 2006; Leyshon, 2010).

The learning agreement

The mentorship relationship has to be based on a learning contract. A learning agreement is frequently used in health professions. It allows the negotiation of what is necessary, wanted and possible in the clinical setting. Students can have vague ideas on what they hope to learn in practice and their learning needs can be nonrealistic or not reasonable. Discussing the learning contract with the mentor both the mentor and the mentee work together towards the same goals and objectives, reducing confusion and conflict during the clinical placement (Casey, 2011; Tichelaar et al., 2013).

The permanent revision of the learning contract allows new formulation or reshaping of the learning objectives, adding to those initially stipulated and imprinting the attitude of the student (Tichelaar et al., 2013).

The portfolio of evidence

During the practice placement the mentee must develop a professional portfolio of evidence (Oerman, 2002; Cooke, 2009; Jones, 2010; Tichelaar et al., 2013). The nursing portfolio is a collection of evidence which document the student's competencies. The documents placed in the portfolio illustrate the background, skills, and expertise of the student (Trossman, 1999). The portfolio documents the nurse's professional development. Reviewing it the professional the person can evaluate how personal and professional goals were attained or not and can plan future developments (Oerman, 2002).

The portfolio is not a substitute for the curriculum vitae, but it provides additional information regarding skills and achievements. A curriculum vitae list the educational institutions attended, the positions held and other background information about the student or the nurse. The portfolio of evidence documents competencies and expertise of the student or the nurse, developed as a result of holding former positions and experiences (Oerman, 2002).

Reflection and learning

Reflection means the description, analysis and thoughts evaluation on a certain topic, suppositions, beliefs, theoretical knowledge and actions (McGrath, 2006; Duffy, 2009). Reflection is important, because it allows us to capture and understand the experience of learning from practice (Tichelaar et al., 2013). Reflection is crucial for efficient practice and can facilitate improvement of the caring process (O'Donovan, 2006; De Sales, 2007).

Reflection can be achieved by discussion or by holding a diary (Levett-Jones, 2007).

A diary is a personal and confidential record of individual experiences. Experiences from the clinical practice are valuable source of self-exploration and analysis. Part of these experiences can last, sometimes as graphic memories, but as time passes most of them fade. In order to understand the significance of these experiences it is important to keep a professional diary, in which facts are described as detailed as possible, associated with accompanying feelings and emotions. This is why students are encouraged by mentors to keep a professional learning diary (Tichelaaret al., 2013).

Students' reflection is encouraged by mentors through positive feed-back and constructive critic. The mentor guides student's reflection process addressing well formulated and specific questions, generally at the end of the working day, in 10 to 20 minutes sessions. The mentee can document these discussions in their professional learning diary (Tichelaar et al., 2013).

At the end of 1990's, European Ministers of Education agreed in Bologna to construct European wide development reforms in all fields of education, including health care education. This process led to several reforms which have explored development phases of education systems in European countries and tried to define the main structure of professional education (Suhonen et al., 2009; Salminen et al., 2009).

During the last decade many of the current European Union (EU) countries, from the former Communist Block (the Soviet Republics' Union and aligned countries) in particular, have undergone substantial re-organization of nursing education that also aimed at the transition of registered general nurse (RGN) training programs from vocational or hospital-based school systems to Higher Educational Institutes (HEIs universities or colleges). The survey of the training of nurses in the EU certified the fact that in 2012 sixteen EU Member States educated general care nurses exclusively at university level (Bachelors' degree) and two Member States had both academic and diploma level education for nurse students in vocational colleges (DG Internal Market, 2012).

It is emphasized that higher education of nurses is a particular phenomenon in the former Soviet Union and aligned countries and it is not further associated only with getting clinical knowledge and skills, but also with the need for the development of professional identity and values, the acquisition of scientific knowledge and the search for its application when implementing the benefits of modern nursing education, humanistic ideas and professional autonomy (Karosas and Riklikiene, 2008).

Increasing globalization has extended to nursing education programs even more as students move from country to country seeking international opportunities and entire programs are being delivered abroad. Internationally moving students, the expansion of

health care service across borders and a highly mobile nursing workforce altogether demand an examination of how we educate nurses for their profession. Numerous national, regional and international research initiatives have focused specifically on the education of nurses and recognize the importance of ensuring not only a sufficient quantity, but also the quality and relevance of health professionals joining the workforce, preparing socially accountable professionals, able to practice collaboratively and to deliver care in current complex and global international context of practice (Barry, 2012; Tichelaar et al., 2012).

Together with modern nursing theories, clinical training in a real health care environment has always been in the center of nursing education supporting students' transition from the "didactic classroom environment to the hands-on clinical world" (Zipp and Colber, 2014). Clinical education experiences support the mastery of psychomotor, cognitive, and affective behaviors needed for competent entry-level practice. Despite the fact that formal mentors in nursing education in the countries under consideration (the Czech Republic, Hungary, Lithuania and Romania) is just a recent practical implication, there is a wide range of international evidence regarding the effective nursing theory and practice integration with changing health care needs and the improvement of educational, psychological and managerial competencies of practicing nurses through mentorship relations (Warne et al., 2010; Tichelaar et al., 2012).

The nursing program providers usually raise the similar questions seeking the improvement and quality assurance of clinical training of student nurses: What are the main features of a good clinical learning environment? What is an ideal duration of a clinical training placement? What kind of mentor-student relationship has to be developed during clinical training? What are the most important elements of good co-operation between HEIs and a health care service organization? There is still a limited number of studies considering these questions in an international context (Suhonen et al., 2009).

The existent situation of clinical teaching and students' satisfaction with the learning environment has been explored in four relatively new member states of EU: the Czech Republic, Hungary, Lithuania and Romania inside the EmpNURS Project (www.empnurs.eu), during the preliminary exploratory phase, and this article describes the results of the exploration. The analysis of the quality and the relevance of clinical training as a substantial part of the nursing programme from students' perspective are important to ensure the acquisition of expected competencies of graduating nurses and strengthen educational systems further by sharing good practices within the EU countries. Finally, evaluation of how we educate future nurses is essential if nursing is to lead the world to better health (Barry, 2012; WHO, 2013).

The decades after the Second World War indicated a period of isolation in few relatively new EU countries of Central/Eastern Europe that joined the Union in 2004-2006. In the Czech Republic, Hungary, Lithuania and Romania, being part of the Communist Bloc influenced many fields of life and science stagnated without cooperation and external links with Western European countries. Nursing in these countries used to be treated as a vocation and was dominated by the biomedical approach to health care and by the medical profession e even though the education processes have been recently moved to universities (Kalnins et al., 2001; Karosas and Riklikiene, 2008). Weaknesses of the independent nursing profession could be seen both in theoretical and clinical studies of nursing, as curricula were strongly

based in biomedicine with the subservient role of nurses to physicians. The instructors of nurse students in medical schools were mainly medical doctors with different specialties, but without an official degree in nursing.

The enlargement of EU linked the strategic reorganization of nursing education in every new European Union member state to the implementation of the Directive of the European Parliament, of the Council on the Specialist Education and the recognition of professional qualifications (Directive 2005/36/EC). This was a real reason for nurses to overcome the traditional stereotype attributed to their profession. The training of nurses was taken more seriously, stimulating action towards the necessary changes mostly regarding the content and duration of nursing studies. Despite the harmonization of nursing education in EU member states, there are still remarkable differences in educational standards and pedagogical arrangements between these Central/Eastern EU countries (Spitzer and Perrenoud, 2006).

After the implementation of the Directive 2005/36/EC, a comparative study on practice education of nurse students in nine Western EU member states was carried out in 2007 and 2009, exploring the factors that enhanced students' learning experience (Warne et al., 2010). The results of this research identified important influences of the national nursing cultural differences on the nurse students' learning environment. There is also one comparative study that included the learning environment of nurse students in Central/Eastern EU countries (Saarikoski et al., 2007) with similar conclusions as Wrane's et al. research, published in 2010 regarding the importance of students' clinical placement.

The most recent evidence from established European countries goes forward and reflects on roles of clinical mentors, students' expectations and their mentorship experience in different settings outside the hospital. International case study research regarding the variation of roles of clinical mentors in eleven EU and non-EU countries shows the absence of a common model of mentors role across the sampled countries recognized (Dobrowolska et al., 2015).

Studies in Sweden focused on student nurses' experience with the clinical learning environment in a nursing home (Carlson and Idvall, 2014) and in primary healthcare (Bos et al., 2015). Their results showed the importance of a good supervisory relationship and their influence on how students experience the clinical learning environment. Qualitative study in Norway reported that learning experiences and motivation of student nurses relates to individual, relational, and organizational aspects. Bachelor students in nursing highlighted the importance of positive relationships between student and mentor under the influence of their own as well as their supervisors' attitudes and competences. In addition, the motivation, self-confidence, and self-respect of students improve when the "feeling welcomed, included, and valued in the ward" is created (Dale et al., 2013).

A study on understanding students' expectations and own experiences of mentorship has been carried out in the UK (Foster et al., 2015). The students were the most positive about involvement of mentors in teaching and explaining, support and supervision, and encouragement. Moreover, the results showed the importance of the support mentors need to provide in the clinical environment.

Despite the expanding the research on mentorship, more international comparative studies on student nurses' clinical training, especially those including the relatively new EU

member states, are still needed. This would allow us to close the gap of information on how and to what extent cultural, organizational and educational differences influence nurse students' satisfaction with their learning results from practice.

In our study we have used the term supervision as to the short time relation between the mentors and students during the survey.

Clinical supervision is fostering self-reflection and self-growth in relation to professional skills (Fowler et al., 2007).We did not know about the real situation and relation between clinical nurses and students in the four involved countries (CZ, HU, LT, RO) and because of this we did not use the term mentorship, which is mostly understood as interpersonal professional relationship between an experienced, more knowledgeable practitioner (mentor) and a less experienced, less knowledgeable individual (protege or mentee), in which the mentee receives career-related and personal benefits (Henry et al., 1994; Dunn et al., 2000; Adams, 2002). Supervision and mentoring are supportive relationships which help individuals to obtain new skill, knowledge and approaches. Each may be accomplished through various models incorporating both basic and specialized skills.

Aiming to describe the situation of clinical placements for student nurses and assess students' satisfaction with the learning environment, this study was carried out with a view to: (1) examine how educational systems of pre-registered nurses occur in four moderately new EU countries e the Czech Republic, Hungary, Lithuania and Romania in the context of clinical training and (2) identify student nurses experience of and satisfaction with their learning environment and supervision by staff nurses during their clinical placements.

This study deals with the situation of clinical placements for student nurses and their satisfaction with the learning environment in four moderately new EU countries (the Czech Republic, Hungary, Lithuania and Romania). The assessment of the results revealed that student nurses were mainly very satisfied with their clinical placement experiences. The structural issues of their clinical placements were quite similar ones than had been found in older EU countries (Warne et al., 2010). Even though then the sample had been collected from 17 nursing schools which have offered degree level programmes in older Europe for many decades, there were only few structural differences regarding how the clinical practice had been organized reported in Warne's et al., 2010 research. The biggest difference was in the supervision model of clinical placements; group supervision model was clearly commoner in this study done in 2013 by Saarikoski et al. than in the study carried out in nine older EU countries, where individualized supervisory model was predominant (Warne et al., 2010).

The duration of the clinical training placement connected with students' utter satisfaction, so that the students with longer placements (7 weeks or more) were more satisfied than the students with shorter placements (under 7 weeks). The mean of placement duration in this study was 10 weeks. This result can be as an interpreted positive feature of nurse education system in new EU countries. One of the most important finding of Warne et al's study (2010) was that students who had longer clinical placements had a higher total satisfaction value than students who had had short placements. In that study the duration of the placement was 6.4 weeks. Similar findings were reported in the other Lithuanian study (Riklikiene and Nalivaikiene, 2013) where the overall assessment of pedagogical atmosphere on the ward positively correlated with the duration of practical placement. It is recognized in

the literature that students' satisfaction and quality of learning can be influenced by many aspects, including how busy clinical areas are and the nature of the practice setting, which can often make it impossible for planned learning opportunities to take place, as the mentor is pulled in many different directions during any one shift. This in accordance with the fact that a short duration of training leaves even more little time to demonstrate skills or talk through events in a meaningful way, highlighting the need to find further ways to support and practice learning in a meaningful and less ad hoc manner (Williams and West, 2012).

The students evaluated the cooperation between their course teacher and the unit with lower scores than other elements of clinical learning environment. Majority (approximately 60%) of the students met their course teacher 1 to 3 times during the placement and communicated also with her or him using e-communication tools (e-mail, text messages etc.). Other studies (Chan, 2002a,b; Gleeson, 2008; Rashid et al., 2015) constantly prove the importance of close co-operation and continual communication between educational and clinical facilities in the planning and evaluation of clinical learning experiences at undergraduate level. Open communication with each other is central to the partnership and aims to promote effective clinical teaching environments for nursing students. Commitment to communicating is crucial to success as it helps to utilize clinical time to its maximum capacity with favorable outcomes to all parties involved.

Supervisory role of staff nurses was very important; the most common (58%) supervisory experience was a successful individualized supervisory relationship and majority of the students kept own staff nurse mentor as the most important professional role model.

The strong point of this study consists in being the first attempt to investigate this area of nursing Bachelors' education with a standardized instrument in new Central/Eastern EU member states and the use of the internet as a communication media. The delivery of a web based addressed questionnaire was more attractive to and more trusted by the students. Clinical training of student nurses shares the similar educational requirements and methodical rules like the practical training of many other health care students at under-graduate level (doctors, dentists, midwives, etc). However, such comparative studies in health care education area are still lacking, firstly because of different instruments used. We presume that the CLES instrument or its broad elements may be adapted to measure satisfaction with the clinical placement in other sample groups of health professions.

However, there are a few limitations in this study. We have not presented any comparisons between the four countries, using statistical tests, because the sub-samples were too small and represented mainly one or two nursing HEIs in each country. Neither do the sub-samples represent a common situation in a current country. Some values describing the sub-samples have been presented in this paper as examples of the most obvious differences between HEIs of different study countries. The small size of sub-samples and the limited geographical areas representation do not allow for any generalizations.

Implications for nursing education in practice

The message for the providers of nursing education in the new and moderately new EU countries is that the group supervision model should shift towards individual supervision, involving in the teaching process more staff nurses instead of ward nursing managers and physicians, even if this represents a good inter-professional cooperation. Likewise, revising the nursing curriculum in order to provide students with longer clinical training periods,

ensuring steady contacts with the nursing teacher or tutor from HEI is undebatable. Positive learning environment that is essential to the effective development of student nurses' practical skills, their personal motivation to learn and to the successful professional socialization must be used as the main quality criterion for institutional internal and external assessment of training process of future nurses.

1.2.5. CONCLUSIONS

The integration progress of EU demands unique education systems in all EU countries and harmonization of nursing education. In some of the new EU member states the lack of perception of nursing as totally independent academic discipline and the still strong influence of medical profession are matters of concern that deeply affect the teaching and supervision procedures of future Bachelors' student nurses in clinical practice, whereas in some other countries more progressive action towards nursing education driven by the nurses themselves are present.

Despite slight educational differences between the relatively new EU member states, the same general practical challenges for nursing educators and clinical nursing staff appear in the effort to change inappropriate and outdated approaches and to develop new educational practices which will better meet student nurses' needs and advance professional identity of clinical nurses. One of the most important issue is the role of clinical staff nurses in this process, the Central/East EU countries, similar to those in this study, should innovate ways to train and support clinical nurses to commit to supervision of Bachelors' student nurses. We suggest the improvement of teaching/learning materials for student nurses (manuals, clinical training diaries, reflection sheets) and continuing professional development programs on mentorship for clinical nursing staff at basic and advanced levels.

CHAPTER 2 - ASPECTS OF COMMUNITY NURSING AND PUBLIC HEALTH

2.1. STATE OF THE ART

Community nursing or public health nursing is a nursing specialization that focuses on public health. Nurses practicing as community or public health professionals unite community knowledge and involvement for the entire population with the individuals' personal and her/his families' experiences of health or illness. Community nurses work in communities and concentrate on different areas, in order to improve the global health status of persons living in that community. The public health nurses investigate possible areas of concern among external factors auctioning in that community and design and plan actions to solve or improve the founded problems. Examples of areas of practice for community nurses include schools, county health departments, correction institutions, and so on. Their activities can include infection prevention and control, health maintenance and education, home care visits and providing home care for persons in need, with chronic illnesses.

Public health is an interdisciplinary domain. Management of health services, epidemiology, biostatistics, environmental health, community health, behavioral health, health economics, public policies, mental health and occupational health, sexual and reproductive health are all subfields of public health. Modern public health practice involves complex multidisciplinary teams which include different health professionals and social workers. These teams can include epidemiologists, biostatisticians, and community nurses and midwifes, microbiologists, economists, sociologists, data managers and physicians, depending on the needs of the community. Different other specialists can be called in, depending on these needs.

There exists a link between economic growth and population's health. In theory, economic growth can allow poor families to spend more money on health and nutritious food for its members. However for this to happen the economic growth has to reach the poor families and those involved must take the right decisions towards consuming healthy food and promote a healthy lifestyle (Lange, Vollmer, 2017)..

Economic growth enables the governments to invest more money in the development of public health and invest in infrastructure, influencing directly or indirectly the population's health. For this to happen it is necessary that tax revenue is enough. It also needs the political decision to invest the exceeding funds in domains that improve health, such as hospitals, medical goods and services, sport facilities. These different steps can go well or wrong, explaining why in different countries with similar income growth things work and in others don't.

Individual increase in permanent income is linked to increased caloric consumption and micronutrients (Lange, Vollmer, 2017).The effect of this rise on health care usage is less clear. Preventive and curative health care services are expensive and there consumption depends upon the social insurance systems.

The relationship between health spending and economic growth is modulated by the level of economic development of the region. Public health spending is sensitive in variations of GDP per capita The effect of public health spending on outcomes is influenced by the institutional environment.

Published evidence suggests that economic growth is not automatically associated with population's health improvement. Additional financial resources are benefic, but it depends on how they are distributed and utilized. Therefore it is important for public health to ensure that exceeding incomes generated by economic growth are used in a manner benefic for population's health.

Disadvantaged people often have poor health. Poor sanitation, improper housing, malnourishment, insecure jobs are associated with health problems, infectious diseases and injuries (Benzeval et al., 2014). Income influences health and does so following four paths: material route, psychosocial route, behavioral route and reverse causation (poor health determines low income) (Benzeval et al., 2014).

The material path is easy to identify and understand: the more money a family has, the more and better services and goods it can buy, having a better life and a better health.

The psychological pathway refers to the fact that the management of a low income is stressful. Comparing oneself with others with a better socioeconomic condition generates negative emotions and feelings. Such an intense and persistent stress can negatively impact one's health and generate diseases.

The behavioral pathway refers to the fact that in people with low income one can notice more frequently unhealthy habits, such as smoking, excessive alcohol consumption or addictions in comparison with people with higher incomes, who demonstrate a healthier lifestyle. This negative habits influence health and on long term generate chronic health problems, such as respiratory diseases, cancers or hepatic problems.

The reverse causation means that poor health can generate unemployment or can prevent people of taking better paid jobs. Poor health in children impacts education and in turn affects future jobs and income.

These four routes are important and interconnected in a complex way that links health and income.

The general context is also important: having a low income in a developed country, with solid social protection is very different than living with a low income in a poorer country, that can't offer to its citizens the same social care.

Hence improving family income in disadvantaged people has always been seen as a way to minimize health inequalities. It is important to understand the ways and mechanisms through which a low income affects health, in order to decide which interventions to improve health should be more efficient.

Material pathways

Money offer people the necessary means for health, such as proper lodging, good sanitation, healthy and nutritious food, warmth and allow people to be socially active. This implies that a basic income level is necessary for a good health. What basic means, is another problem, can change over time and have different meaning in different economic or geographical context. This also suggests that the more money one has, the better health is. This is not always so, because sometimes more money can determine negative behaviors and, in time, chronic health problems. However a better income means people can afford better goods and services, including high quality health services.

A high family income allows parents to offer better education to their children, private schools and a possible better future, including higher paid jobs and social position.

The wider economic context in which a person lives is also important. Some countries offer public health services and education for people with low income, and also social support for unemployed persons.

Psychosocial pathways

The way social environment makes people feel generate psychosocial effects.

Living with a poor income is stressful. It can also generate a lower support from family and friends and certainly doesn't help them to cope. Feeling a lower social status accentuates the distress and can induce on long term biological changes in those individuals, favoring the development of stress associated diseases, such as hypertension, coronary heart diseases or cancers.

Behavioral pathways

In socially disadvantaged individuals unhealthy behaviors are more frequent. There are more reasons for this. Some healthy behaviors are expensive. A healthy diet is more expensive than junk food, going to gym and extracurricular sports cost money. People with low income may try to cope with their social position through alcohol or somking, not thinking to future consequences of their habits.

Cultural context is also different for different income levels.

The degree of acceptance for unhealthy behaviors or the grade in which health promoting messages are understood and accepted varies in different social media. An increased income without broader behavioral changes can't promote a better health.

The reverse causation – poor health leading to a low income

Individuals' health impacts income. Illness makes people unable to work and reduces income. An ill health as a child can have educational consequences, diminishing potential employments and better paid jobs opportunities.

Other factors

Other factors that influence health and income are intelligence and personality.

Intelligence generates educational advantages, with better chances for a good employment and better income and also facilitates the choice of healthy habits and life-style, reflected in a better health.

The above cited factors and mechanisms are interconnected across people's lives in ways that influence health. These factors suggest the need for a wide range of policies to ameliorate heath inequalities (Benzeval et al., 2014).

Parental income is important for children's health, having long term impact on future social, economic and behavioral aspects as adults and the resulting health.

In conclusion, even if there is a strong link between economic growth, increased personal income and health, the pathways by which this connections operate have to be known and better understood, in order to allocate additional resources for those in need.

My interest in public health and community nursing is featured in the following articles:

- Cărăuşu Elena Mihaela, Paris S, Burlea LS, Tucmeanu AI, **ANTOHE I** . The Crisis Impact on the Romanian Health System and Population Health. Revista de Cercetare şi Intervenţie Socială/ RCIS, 2017, 57, 120-37, ISSN: 1583-3410 (print), ISSN: 1584-5397 (electronic).
- Cărăuşu ME, Burlea LS, Lupu IC, **ANTOHE I**, A study on the cognitive level of health education for secundary school students from the rural environment Revista de cercetare şi intervenţie socială, 2016, 55: 19-30 (ISSN 1583-3410 (print); ISSN 1584-5397 (electronic).
- Cărăuşu EM, Dascălu GC, Zegan G, Burlea LS, Lupu IC**, ANTOHE I**.The general and oral health status in older adults from rural environment of Iasi County, Romania. Revista de cercetare şi intervenţie socială, 2017, 59: 187-208 (ISSN 1583-3410 (print); ISSN 1584-5397 (electronic).
- Botnariu EG, Popa AD, Nechifor IE, **ANTOHE I**. The main barriers to insulin treatment in elderly diabetic population: the role of therapeutic education. Revista de cercetare şi intervenţie socială, 2017, 56: 70- 8 (ISSN 1583-3410 (print); ISSN 1584-5397 (electronic).
- Botnariu EG, Forna NC, Popa AD, ANTOHE I, Lăcătuşu C, Mihai B. Presepsin as a Biomarker for Sepsis Evolutions in Diabetes. Revista de Chimie (Bucharest), 2016, 66 (12): 2057-9 (ISSN: 2537-5733; ISSN-L: 1582-9049) (http://www.revistadechimie.ro)

2.2. **HOW MONEY IMPACTS HEALTH**

2.2.1 I**NTRODUCTION**

The financial crisis began in USA in the autumn of 2008 and rapidly degenerated by contagion everywhere, becoming a global economic crisis in the next year. The causes generating the crisis were not corrected, despite all declared efforts (Georgescu, 2012). The Commission on Social Determinants of Health of the World Health Organization (WHO) has examined the global conditions of the economic crisis and elaborated a Report on the crisis impact upon vulnerable groups, addressed to the governments (Parry & Humphreys, 2009). The economic crisis in Romania had an important negative impact because the Romanian

health system had already a lower than needed resources level (Forna and Gribincea, 2014; Agheorghiesei et al., 2013).

The aim of our study was to analyze the impact of the crisis upon the Romanian health system and to reveal the efficacy of the austerity policies implemented to control the negative consequences of the crisis.

The specific objectives of the study were: (1) To assess the crisis impact upon the Romanian health system (main social determinant of health); (2) To describe the effects of the changes in the Romanian labor market and the working force factors (unemployment, reduced perspectives of re-engagement, low revenue after paying taxes) on life conditions, life style and the health of population; (3) To evaluate the results of the austerity policies and anti-crisis measures on the health system.

We conducted a retrospective study, the vulnerable indicators of the crisis were selected and classified into two categories: indicators evaluating the crisis impact on the health system and indicators evaluating the impact of the anti-crisis measures and austerity policies.

Firstly the paper highlights the crisis impact on some socio-economic determinants of health discussing the most important macro-economic indicators registered in Romania during 2008-2014 period of time with the aid of descriptive statistics and comparative analysis.

Secondly the paper pinpoints through comparative analysis the crisis impact on the population health status, depicted by the European Core Health Indicators (ECHI) as health system outcomes.

The economic-financial impact of the crisis was studied using as method a comparative analysis of the health services financing, the health programs financing and the consumption of compensated medicines from the National Health Insurance Fund (NHIF).

The political impact was evaluated by the analysis of the efficacy and consequences of the austerity policies targeted at lowering the global crisis effects. The study was limited to the available European and national data sources.

The determinants of health are classified into four groups: factors concerning human biology; environmental factors; macro-economic and socio-economic, cultural, educational; health system factors (Zanoschi, 2003). Each group includes direct and indirect determinants. The main direct determinants refer to human biology, life style (smoking, diet, alcohol drinking, drugs intake), physical and social environmental conditions (housing, the access to potable water and the hygienic conditions) and social group behavior (violence). Social determinants of health are those social conditions (and their population distribution) which influence individual and group differences in health status. The main social determinants of health are: unemployment, low social status, poverty/social exclusion, Gross Domestic Product (GDP), the socio-demographic alterations in the population structure, crisis situations etc.

2,2,2, **SOCIAL DETERMINANTS OF HEALTH**

The crisis impact on the main socio-economic determinants of health

Starting with 2008, on the international market there were signals announcing that "the economy is facing a new economic-financial crisis…" (Lin, 2008). These signals came from the economic evolution of developed countries (USA, Great Britain, Spain, etc.).

The impact of the crisis on the economic growth

The synthetic indicator of the economy evolution is represented by the Gross Domestic Product. Romania had an increased rhythm of GDP during 2007–the former half of 2008, greater than other EU countries. The data published by National Institute of Statistics (INS) indicate that, after a 7.34% real increase in GDP, in 2008 compared with the previous year (Table 2.1), the economic crisis has been stronger in Romania than in other EU countries and slowed down the growth of the GDP to 6.576%, in 2009.

Table 2.1. The Gross Domestic Product of Romania

Indicators:	**Year**						
	2008	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**
GDP (Billions RON)*	503.9	491.3	523.6	556.7	587.5	623.3	669.5
GDP (USD Billions)	204.335	164.345	164.436	189.775	169.395	169.180	189.660
GDP (Billions €)	139.765	118.196	124.328	131.327	131.747	144.2	151.9
The annual variation (%) of GDP	+ 7.34	- 6.576	- 1.149	+ 2.159	+ 0.689	+ 3.53	+ 2.9

Source: *National Institute of Statistics (NIS); World Bank (2013): data.worldbank.org/indicator NY, GDP

The straightening out rhythm of GDP remained low during the following years, due to the contagion effect within the Euro-zone (Sinca, 2013). This slow recovery suggests that the crisis left lasting scars in the Romanian economy. The Gross National Income per capita indicator (GNI/capita) best reflects the country well-being. This indicator registered one of the lowest values in 2010 (€5.689); in Romania, it registered lower values (49%) than the EU-27 average. Significant differences in the GNI/capita value are to be found between the Romanian regions. The North-East region recorded the lowest value; there were only two regions (Bucuresti-Ilfov and the West Region) which exceeded the national average to this indicator.

2.2.3. **THE SOCIAL IMPACT OF CRISIS ON ROMANIAN POPULATION**

The crisis impact upon the work force

The global crisis had an important negative impact on the structure of the work force, bringing about the rise of unemployment alongside with the reduction of the occupied population. After the economic rise, registered during 2005-2008, starting with 2009 the occupied population began to fall reaching in 2011 the lowest ever registered value. The decrease was the result of many causes, as following: economic crisis that led to bankruptcy of many companies; the movement of certain companies with foreign capital in other areas with lower level of the taxes etc. The number of employees from the public sector registered a decrease starting with February 2009. The private sector accounted for 66.2% of the

employees in 2011 (NSI, 2012). For the next period a slow increase of the number of employees is expected, due to the hope on the Romanian economy revival.

All aspects related to the work force have an important influence on the population health. Unemployment is associated with increased poverty risk/social exclusion, poor mental health and suicide (Dima-Cozma et al. 2014).

The lack of revenue has the strongest effect (European Commission, 2011). The number of unemployed people was 709,383 in Romania, in December 2009 (Table 2.2). There was a decrease of the unemployed to 493,775 persons until December 2012. The registered rate of unemployment in 2011 and 2012 was established to 5.12%, respectively 5.59%. This was partially due to the elimination of the school and faculty graduates, whose period of payment expired (ANOFM, 2012).

Table 2.2 The unemployment in Romania in the period 2008-2014

Indicators:	**Year**						
	2008	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**
Registered unemployed (persons) December	403,441	709,383	626,960	461,013	493,775	512,333	478,338
Registered unemployment rate (%) ANOFM	4.4	7.8	6.87	5.12	5.59	5.85	5.29
Unemployment rate (%) ILO report	5.79	6.89	7.28	7.40	7.04	7.31	7.17

Source: http://www.anofm.ro

The unemployment rate published by the International Labor Office (ILO) differs, because the unemployment rate is calculated as a percentage of the unemployed from the active population.

The crisis impact on poverty risk

In European view, "there are considered to be poor, those persons, families or groups, whose resources (material, cultural or social) are so limited that excludes them from the minimal life standards considered to be acceptable in the societies where they live". The European Union used a relative definition of poverty: a person is poor if he/she has "an income under 60% of the mean national income available" (Antuofermo & Di Meglio, 2012). Poverty is one of the most important social determinants of health. In case of illness, the poor persons make important direct expenses for health and associated services, exceeding 40% from the entire household expenses. These people are exposed to the risk of losing the health rights, because they can't afford to sustain the private expenses associated to health care (Dragomiristeanu, 2010; Gavrilovici, Oprea, 2013). According to the latest data from

EUROSTAT, in 2013, 24.5% of the population (or 122,600 thousand people), in the EU-27 were at risk of poverty or social exclusion. In 2012, 24.8% of the population (124,200 thousand people), were at risk of poverty or social exclusion, compared with 24.3% in 2011, but is higher than in 2008 (23.6%).

One of the five headline targets of the Europe 2020 strategy is to reduce the number of people living at risk of poverty or social exclusion by 20 million by the year 2020. The Eurostat data shows that in the2008-2013 period, Romania registered highest rates of poverty risk or social exclusion, but the at-risk-of-poverty/social exclusion rate has slightly decreased from 2008 to 2013 (from 44.2% to 40.4%) - Table 2.3.

Table 2.3. Indicators of the poverty risk/social exclusion

Indicators:	**Year**					
	2008	**2009**	**2010**	**2011**	**2012**	**2013**
EU27- poverty risk (thousand persons)	115,694	113,773	116,206	119,758	124,200	122,600
EU27- poverty risk/social exclusion rate (% from EU population)	23.6	23.1	23.5	24.3	24.8	24.5
EU27- Severe material deprivation (%)	8.5	8.2	8.4	8.8	9.9	EU28-9.6
Romania- poverty risk (thousand persons)	9,420	9,112	8,890	8,630	-	8,600
Romania- poverty risk/social exclusion rate (%)	44.2	43.1	41.4	40.3	41.7	40.4
Romania- Severe material deprivation (%)	32.9	32.2	31.0	29.4	29.9	28.5

Source: Eurostat. ec.europa.eu

According to the Europe 2020 Strategy, the Government of Romania has set an ambitious national target of reducing the number of poor and socially excluded by 580,000 people (Eurostat, 2014). The main causes with a negative impact on poverty are the high level of unemployment and the lower level of the income. Romania had the highest rate of poverty risk of the working persons from Europe (17%) in 2008, before the crisis debut. The situation was more difficult in 2012, when the poverty rate of the working persons was double compared with the EU27 average. Romania continues to be the bottom of the table of minimum wages in Europe, show the Eurostat report (Eurostat, 2013).

Poverty has an important territorial dimension in Romania, affecting especially the population from the N-E, S-E and S-W regions. Besides maintaining a low level of income among members of a community, poverty includes limiting access to services such as education, health, decision-making and lack of communal facilities like water, sanitation, roads, transport and communication. In 2010 Romania ranked fifth in the EU in regard to income inequality. With a Gini Coefficient of 33.3,

Romania was placed among the most unequal countries in EU, having a level of income inequality significantly higher than the EU-27 average (30.4) (Eurostat, 2013).

2.2.4. THE CRISIS IMPACT ON THE ROMANIAN HEALTH SYSTEM

The sub-financing of the health system is an old issue. The health spending share in 2008 placed Romania on the last place in Europe. The same situation was maintained in 2009 and 2010, when the health spending share was respectively 5.68% from GDP (WHO, 2011: 132). The health spending share from the GDP rose to 8.9% in the EU, in 2010. The relevant indicator of the financing of the health system is the health spending per capita (per inhabitant). The total spending for health per capita was 400.8 $USA in 2008, placing Romania on one of the last places in EU. A critical analysis reveals that Romania decreased the level of the contribution to the social health insurances in the economic crisis period, in 2008 (from 12.5% to 11%) and 2009 (to 10.7%).

The financing of the primary health services

The primary health services are provided in Romania by the individual family health offices. Social Health Insurances settled contracts with 11,388 family doctors (GPs) in 2009. Over 94% of the total population was registered to GPs. The primary health assistance received limited revenue during the crisis period: in 2008 the primary health services received 1.13 bln. RON (10.28% from NHIF); in 2009, 1.1 bln. RON and 1.19 bln. RON (12.4% from NHIF), in 2012. All these values were under EU27 average value of 25%.
Family medicine received in 2009 a budget lower with 24% than 2008. The diminishment of the revenue was generated by the decrease of the value of the point, from 4.66 RON (in 2008) to 4.25 RON (in 2009), and the decrease of the fee service from 2.34 RON (in 2008) to 1.50 RON (in 2009). During the former half of the year 2012, the point values, used to calculate the primary health services payments, were of 3 RON and 3.5 RON for the last 2 terms.

The financing of the secondary health services

The secondary health services are formed of specialty and laboratory medical services offered in outpatient settings, in consulting rooms, ambulatory sanitary units, medical laboratories, diagnostic and treatment centers and multifunctional medical centers. All these sectors settled contracts for the delivery of medical services with the social health insurances. The National Health Insurance Fund settled 2,744 contracts with specialty offices and ambulatory medical units (including 11,400 physicians) during 2009. The revenue used by NHIF in 2009 for secondary health services was 2.15% (320,000 000 RON) and 2.15% (380,000 000 RON) in 2012 (CNAS, 2012).

The financing of hospital services

The third level of medical assistance is delivered in sanitary units with beds (hospitals), under the form of continuous assistance or day care. This is the domain with the greatest population addressability, and the most expensive sector of the Romanian health system. The health system had inherited an over-dimensioned hospital sector, together with inflexible financial and institutional rules. There were 503 hospitals, 430 of which being

public hospitals (370 subordinated to the County Council and Mayor's Office) in 2010, in Romania. The hospitals sector spent the most part of the NHIF budget (44.8% in 2008 and 47.7% in 2009), augmented by HM funds for infrastructure interventions, medical equipment supply, together with the local public authorities given funds. The spending was 7.58 bln. RON (41.9% from NHIF), from which 7.49 bln. RON (41.63%) for general hospitals, but half of this spending was allocated to the 67 emergency hospitals in 2012. In table 5 we underline the significant decrease of the nominal spending of the hospitals. In Romania there existed 12 private hospitals in 2006, but in 2012 their number increased to 86. Forty private hospitals were in contractual relationship with NHIF in 2009, but in 2010 there were 52. The private hospitals received from NHIF 150,703,000 RON in 2011, increasing with 40% the next year, in 2012 getting to 213,500,000 RON (CNAS, 2012).

The movement of funds from the public sector towards the private one determined the reduction of the NHIF spending for public hospitals with 10% in 2012.

The financing of the national health programs

The national programs have the legal aim to prevent and treat some illnesses with major impact on the population health and in some cases (AIDS, tuberculosis) with high epidemiological risk. These programs are financed from the State Budget and NHIF after the Budget Law is adopted every year. The spending on the health programs was 10.8% in 2008, 14.1% in 2009 and 12.8% in 2010 from the total NHIF.

The greatest number of beneficiaries from the health national programs in 2009 was enrolled in the Diabetes Program (565,000 patients), followed by the Oncology Program (97,000 beneficiaries). The subprogram for Treatment of Tuberculosis included 42,000 people, the Program for Cardiovascular Diseases included 29,000 patients and the Program of Endocrinology included 22,000 patients. Other beneficiaries were included in the Subprogram for Persons with AIDS Treatment and Monitoring (15,000 patients), in the Orthopedics (11,000 patients) and Renal Dialysis (10,500 patients) (CNAS, 2012).

The crisis impact on the long term sustainability of the social health insurances The Romanian population uses more medical services than the social insurances availability allows. The NHIF, the main financing source of the Romanian health system, proved not to be financially sufficient. A deficit of 1,900,000 million RON it was registered in 2008, 2,150,000 million RON in 2009 and 4,290,000 million RON in 2010 (0.7% from GDP). These sums were covered by transfers from the State Budget.

The crisis impact on the health of the population

Romania suffered great economic, political and social imbalance during the crisis, with significant impact on the population health. The degradation of the health of the population was due to the economy fall, determined by the crisis itself and its consequences (the increase of the unemployment, the worsening of the life level, the sub-financing of the health system, and the impairment of the quality of the health services). The performance of the Romanian health system is one of the lowest in the EU, especially regarding the main European Core Health Indicators (ECHI) as health system outcomes (WHO, 2010). The

consequences are evident at the general population level. The crude birth rate had a decreasing tendency during the analyzed period. The new socio-economic reality generated the decrease of the crude birth rate and maintained it at low values. The EU27 average value of this indicator was 10.7 ‰ (in 2009); while in Romania the value was under the average European level (10.4‰ in 2009 and 9.2‰ in 2011) (INSP, 2011). This aspect is explained by the precarious socio-economic conditions, the low living level of the population (Untu et al., 2015) and the emigration increase. Romania is among the countries with high mortality level, even if during 2009–2012 the crude mortality rate was stabilized around the value of 12‰. Infant mortality is an important demographic phenomenon and also a significant indicator of the socio-economic development (INSSE, 2013). Romania had one of the highest infant mortality rates in Europe (9.4‰ in 2011). This indicator had great regional disparities; the N-E region registered the greatest value of this indicator (14.2‰). The values for rural area are greater (11.8‰) than those of urban area (7.5‰) for the same indicator (Dragomiristeanu, 2010). The age adjusted mortality rate through all causes (954.4/100000 inhabitants in 2009, respectively 1198.8 in 2012) was greater than the EU27 average (601.2/100000 in 2009). The cause-specific mortality rates by cardiovascular diseases, cancers and digestive diseases were high in Romania starting with 2009 (INSP, 2011). The cardiovascular diseases represented the first mortality cause (548.4/100000 inhabitants in Romania towards the EU27 average of 216.8/ 100000 inhabitants). A quarter of this value was registered in persons under 60, in 2009. Although in EU the cancer mortality trend decreased, in Romania the standardized mortality rate value for cancer significantly increased from 181.3/100000 inhabitants in 2009 to 230.2/ 100000 inhabitants in 2012. The standardized mortality rate through digestive diseases was high (75.4/100000 inhabitants in 2009) compared with the average level in EU27 (62.0/100000 inhabitants in 2009). The mortality through hepatic diseases was the highest in EU27 in Romania, in 2009. The crises acted very different in different European countries, it played out in a variety of modes and has not equally affected all countries (Thomson et al., 2014).

As a result of the economic impact of the crisis some countries experienced an important and sustained decline in their GDP. One of the most important consequences was the quick increase of unemployment rates in some states, many households and families having to face a growing financial pressure and feel insecure.

Mental health problems proved one of the most sensitive health indicators affected by the economic changes. Community support decreases during crisis and people who previously had borderline psychiatric affections develop overt psychiatric diseases during crises, due to stressful and persistent conditions, perceived as adversity.

Suicide rates have increased in some European countries. In most the former descendent trends was reversed, evolving ion parallel with the ascending trend of total cases of psychiatric illnesses.

There is evidence that unemployment, poor living conditions and financial pressure and insecurity are related to the increment of psychiatric illnesses (Thomson et al., 2014).

Behavioral risk factors for mental diseases reveal different developmental patterns. It seems that alcohol consumptions increase in people who already are heavy drinkers and in those experiencing unemployment. No study could find a constant association between drinking alcohol and increased suicidal risk.

There are certainly other adverse effects of factors, such as financial insecurity, improper health service access and discontinuity in health services for chronic diseases, that impact population's health status.

This is why strict monitoring at national and international level is requested, generating policy decisions and actions able to limit these effects. Failure of these efforts means considerable loss and sufferance inhuman and economic domains (Thomson et al., 2014).

The economic crisis confirmed what was already known from past experience and from common sense: economic decline represents a threat to health and quality and efficiency of the health systems.

Economic shock increases the need of health care, but carries the difficulties in the accessibility to care, especially in disadvantaged people categories.

Economic shock generates fiscal pressure, put pressure on governmental finances and stress more a sector in which people rely on public health sector.

The negative effects of crisis on health are better seen in people unemployed and efforts should be made to alleviate it through public policies (Thomson et al., 2014).

A high level of the avoidable deceases was also registered. Alcohol abuse also generates circulation accidents, cardiovascular diseases, hepatic cirrhosis (INSP, 2011) and homicides (2.2/100000 inhabitants in 2009, compared with the average EU27 of 0.9/100000 inhabitants). Romania registered a high morbidity rate as a direct consequence of poverty, low educational and living standards (Anton, 2012). Infectious diseases, such as hepatitis (type A–17.35 new cases/100000 inhabitants, compared with EU27 average of 3.47, in 2009), tuberculosis (108.2 new cases/100000 inhabitants compared with the EU27 average of 15.9 in 2009) and sexually transmitted diseases, especially syphilis (18.7 new cases/100000 inhabitants, compared with EU27 average of 3.7 new cases/100000 inhabitants) were high as before crisis. The Romanian state paid more than 2 million sick leaves, with over a thousand million RON, for morbidity with temporary work incapacity in 2012. Life expectancy at birth is one of the key indicators which measure the health and the development state. In Romania, life expectancy at birth for women was 77.4 years and for men 69.8 years (in 2009 life expectancy at birth in the EU was of 76.4 years for men and 82.4 for women) (INSSE, 2013). A study of the Economic Prognosis Institute (IPE, 2011) of the Romanian Academy, with the aid of PhRMA-Local American Working Group, shows that Romania loses about €18,600 000 million, representing 15% from the 2010 GDP, because of the precarious health state of the population. Romania could have a plus of €6,700 000 million in revenue if the health state of the population were the same as the EU27 average. This could happen if the Romanian health system will receive 8.5% from GDP in the next ten years.

2.2.5. THE AUSTERITY AND ANTI-CRISIS MEASURES

The Government introduced some budgetary and structural reforms, trying to lower the crisis effects during 2009 and 2010, but these were not enough to resist against the global pressures and to attract foreign investors. In 2010 the Romanian Government signed a financial accord with the International Monetary Fund (IMF), the European Commission (EC) and the World Bank, with a value of €19,950 000 million, for 24 months (IMF, 2013). The program helped to regain confidence in the Romanian economic perspectives. The

governmental measures taken in Romania in order to lower the crisis effects and to stimulate the economy were: the allocation of 6.3% from GDP for investments in 2009 and 6.4% in 2010, the state warranties (2,600 000 million RON in 2010) for the co-financing of the infrastructure projects from European funds. Social policies were implemented to reduce unemployment and to sustain the business environment, like reducing the social contributions of the firms engaging unemployed people.

The austerity policies and their effects

Austerity policies were implemented in Romania to reduce the effects of the crisis, but the population's perception was that these were fragmentary, implemented without much analysis and relatively inefficient. Salaries were the first target of the austerity measures, Romania being among the countries with the greatest salary fall from the EU. The salary reduction was "a key instrument or a correcting mechanism within internal devaluation politics"… This tendency did not solve the competitive problem, but worsened the existing problems, affecting the most vulnerable". McKee Martin, from the European Observatory on Health System and Policies declared that one of the important challenges concerns "the ignorance of the medical effects of the crisis, even if they are very visible" by the governmental factors (Karanikos et al., 2013). The efforts of the government to reduce the impact of the crisis make people less healthy, causing high morbidity and mortality rates, because the Romania people search medical support in an advanced stage of their diseases (when it is too late, or too costly). Health is the key factor for the economic and social well-being. The health state of the general population and of the work force is essential for a competitive country. A good health state determines the increase of the productivity, and this is the engine of the long term economic increase. Employees with precarious health cannot work with their whole potential. This generates negative outcomes in the economic activity, and supplementary costs for social budgets.

2.2.6. **CONCLUSION**

Investment in Romanian health system is vitally important for health of the general population, as a key strategy for boosting the economic development.

The negative effects of crisis on health are better seen in people unemployed and efforts should be made to alleviate it through public policies

2.3. **THE GENERAL AND ORAL HEALTH STATUS IN AN ELDERLY RURAL POPULATION**

2.3.1. INTRODUCTION

Community nursing includes health education and therapeutic education of different population groups, in order to enhance wellbeing and health in the community.

Oral and dental health care connected with general health, because they share same risk factors, such as smoking, diabetes mellitus or low educational level (Cullinan et al, 2013). There is a mounting body of evidence that links periodontal disease to cardio-vascular disease (Katz et al, 2001; Buhlin et al, 2002), especially coronary heart disease (Stiles., 2024; DeStefano et al, 1993; Ryden et al, 2016; Busko, 2016) and other chronic diseases, such as type 2 diabetes mellitus, rheumatoid arthritis or cerebral vascular disease (Harrison, 2014). In an adult Swedish population with periodontitis (after adjustment for smoking, diabetes, education and marital status) the risk for a first myocardial infarction was 28% higher than in a matched population without periodontal disease (Ryden et al, 2016). There is a strong evidence for the association of periodontitis and coronary heart disease, but this does not prove causation (Busko, 2016).

Our study was *motivated* by the lack of recent data about general and oral health status in rural elderly.

Such type of study provides valuable information which is necessary for the national and local policy makers.

The data allow assessing the opportunity of health programs integrated at community level, designed to solve the main health problems emphasized in geriatric population from the rural environment and to estimate the resources required for their implementation.

The *aim* of our study was to evaluate the health status in older adults, aged 65-74, from a rural community of Iasi County, in North Eastern region of Romania, in order to identify the main general and oral health issues.

The main *objectives* of our study were:

(1) to evaluate the oral morbidity, the oral health related behaviors and the attitudes towards oral health;

(2) to evaluate the general morbidity;

(3) to study the addressability to health services.

2.3.2 MATERIAL AND METHODS

The studied group was selected from a rural community with 4975 inhabitants, 1712 (35.51%) out of them being 65 to 74 years old.

Initially, our study involved 208 individuals, during January to December 2016. The global response rate was 94.23% (5 persons left the study because they changed their residence and 3 died during 2016). Finally, the studied group included 196 persons and it was statistically representative (accepted maximum error was ±2.58%) for the geriatric population

from rural environment of Iasi County.

The *study protocol* was designed according to the methodology of prevalence studies. The data collection was carried out following the main directions:

(1) a clinical examination (general and oral). All subjects were examined by a physician and information on their general and oral health status were recorded;

(2) a questionnaire with 21 items that targeted: the self-perceived overall health; the self-related oral health; the addressability to health services. The value of Cronbach alpha coefficient for the questionnaire was 0.724.

The following demographic and socio-economic factors were considered as *independent variables*: gender (masculine/feminine), age, marital status, living arrangements (referred to the place in which the old persons stayed, the type of family in which they lived and the people they lived with), the educational level and personal monthly income.

The *dependent variables* registered in our study were: the general morbidity indicators, the oral morbidity indicators, the addressability to health services, the supplying medicines, the self-perceived overall health, the self-related oral health (SOH) and the use of dental prosthesis. The oral health related behaviors (the using of dental services during the past 2 years, smoking and alcohol use) and the oral health attitudes were also assessed.

The *descriptive analysis* was used to assess the general morbidity and oral morbidity indicators.

To evaluate the gender differences in the prevalence of general diseases and oral health outcomes we used *analytic statistic methods*. Odd Ratio (OR) and Attributable Risk (AR, or risk difference) with 95% Confidence Intervals (CI 95%) were used as measures of association between demographic and socio-economic factors considered as independent variables and health indicators as dependent variables. To assess the significance of the identified differences we performed the Chi-squared test (Pearson χ^2); p value < 0.05 were considered to be statistically significant.

2.3.3 RESULTS

The morbidity of older adults from the rural environment, dominated by the non-communicable diseases, determines general and oral health and social problems that are difficult to manage.

Analysing the age structure of the studied group, one can notice that most of the subjects (68.88%) were part of the age group 65 to 69 years.

The main results regarding the ***general health outcomes*** are depicted in Table 2.4.

In the male gender individuals, the model of the general morbidity is dominated by cardio-vascular diseases, diabetes mellitus, osteoarticular diseases, accidents and traumas, chronic digestive and respiratory diseases.

The main risk factors identified were: comorbidities, smoking, added salt and excessive alcohol consumption.

The general morbidity in female gender is dominated by cardio-vascular diseases, diabetes mellitus, osteoarticular diseases, chronic digestive and respiratory diseases.

The identified risk factors were the same as for the male gender.

Older adults with diabetes mellitus had also periodontal disease.

Table 2.4. General health outcomes in elderly from rural environment- *by gender*

Age group: ***Gender:***	**65-74 years**						**Odds Ratio** (*CI 95%)*	**Attributable Risk** (AR)
	Male		**Female**		**Total**			
	n_1	(%)	n_2	(%)	N	(%)		
	68	43.87	87	56.13	155	100.00		
General health outcomes[Item code of data base]:								
Prevalence of cardiovascular diseases:								
-correctly treated [1];	43	63.24	59	67.82	102	65.81	OR=0.82	
-intermitent treatment [2];	16	23.53	32	36.78	48	30.97	(0.42-1.59)	
-recently diagnosed [3].	13	19.12	10	11.49	23	14.84		
	14	20.59	17	19.54	31	20.00		
Prevalence of chronic digestive diseases	23	33.82	21	24.14	44	28.39	**OR=1.61*** (0.8-3.24)	AR=0.3789
Prevalence of diabetus mellitus:	20	29.41	28	32.18	48	30.97	**OR=1.27***	AR=0.2126
-correctly treated [1];	12	17.65	15	17.24	27	17.42	(0.64- 2.51)	
-recently diagnosed [2].	8	11.76	13	14.94	21	13.55		
Prevalence of obesity	15	22.06	21	24.14	36	23.23	OR=0.89 (0.42-1.89)	
Prevalence of chronic rheumatic and osteo-articular diseases	19	27.94	27	31.03	48	30.97	OR=0.86 (0.43-1.73)	
Prevalence of trauma and accidents	18	26.47	9	10.34	27	17.42	**OR=3.12*** (1.3-7.49)	AR=0.6795
Pearson $\chi^2_{\text{calculated value}}$ and *p* value:	χ^2=6.8996		df=1		*p*=0.008621**			
Prevalence of chronic renal diseases	5	7.35	11	12.64	16	10.32	OR=0.55 (0.18-1.66)	
Prevalence of chronic respiratory diseases	16	23.53	13	14.94	29	18.71	**OR=1.75*** (0.78-3.95)	
Prevalence of neuropsyhic conditions	4	5.88	3	3.45	7	4.52	**OR=1.54*** (0.33-7.15)	AR=0.3506
Prevalence of more than 2 chronic diseases in same subject (co-morbidities)	41	60.29	50	54.94	91	58.71	**OR=1.12*** (0.59-2.14)	AR=0.1071
Elderly with special needs:	8	11.76	5	5.75	13	8.39	**OR=2.0148***	AR=0.5036
-motor special needs [1];	5	7.35	4	4.60	9	5.81	(0.63-6.39)	
-sensorial special needs [2];	2	2.94	1	1.15	3	1.94		
-psychiatric special needs [3].	1	1.47	0	0.00	1	0.65		
Smoking prevalence:	27	39.71	15	17.24	43	27.74	**OR=3.16***	$AR_{[1]}$=0.6835
-more than 20 cigarettes/day [1];	19	27.94	5	5.75	24	15.48	(1.51-6.62)	
-10-19 cigarettes/day [2];	8	11.76	11	12.64	19	10.97		
-former smokers [3].	8	11.76	9	10.34	17	10.97		
Pearson $\chi^2_{\text{calculated value}}$ and *p* value:	χ^2=9.7505		df=1		*p*=0.001793**			
Prevalence of daily alcohol consumption (over 200 ml/day)	23	33.82	11	12.64	34	21.94	**OR=3.53*** (1.57-7.92)	AR=0.7167
Pearson $\chi^2_{\text{calculated value}}$ and *p* value:	χ^2=9.9987		df=1		*p*=0.001567**			
Added salt:								$AR_{[1]}$=0.4872
-yes [1];	24	35.29	19	21.84	43	27.74	**$OR_{[1]}$=1.95***	
-dietary low sodium intake [3].	12	17.65	19	21.84	31	20.00	(0.96-3.98)	

Odds Ratio (OR); *CI 95%- C*onfidence *I*nterval 95% for OR; AR- Attributable Risk; *Statistically significant for *p*<0.05; **Statistically significant for *p*<0.001.

Addressability to general and dental health services

The main results of the addressability to dental medicine services and self-perceived oral health in elderly studied group reviled that in 44.39% cases dental services were accessed in emergency, 5.10% were not programmed and half of consultations (50.51%) were programmed. Last dental consultation was not remembered by 14.80% patients, happened one year ago in 48.98% of subjects, was 2 years ago in 23.98% of cases and more than 3 years ago in the rest of patients (17.35% cases).

Self-perceived oral health was assessed as good by 4.67% of patients, good by 9.18% of cases, average by most (47.45%), poor by 23.98% of subjects, very poor by 14.29% of persons and was not known in a minority of cases (1.53%).

Avoidance of dental services was motivated by lack of financial support in most patients (57.14%), difficulties in walking in 20.92% of patients, neglect (10.71%) or fear in 9.69% of cases and remained unknown in 1.53% of cases.

The main factors that determined an *avoidance of health services by male patients* are: lack of money, difficulties in walking, negligence, fear of pain and low educational level (under 8 classes).

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The main factors that determined an *avoidance of health services by male patients* are: lack of money, difficulties in walking, negligence, fear of pain and low educational level (under 8 classes).

The *avoidance of health services* profile for female elderly persons is linked to the same factors identified in the case of male gender.

The main motives that determined presentation to the dentist were: pain in most of cases (30.10%), difficult mastication in 18.37% cases, adjustment or repair of denture in 15.82%, complex oral rehabilitation in 6.63%, oro-dental infection in 5.61% and trauma in 3.57% of patients.

2.3.4 DISCUSSIONS

The North-Eastern region of Romania is the area with the highest number of inhabitants, with a mean population density of 100.2 inhabitants/ km^2, that exceeds the mean value of 89.5 inhabitants/ km^2, for the entire country.

In North-Eastern region, Iasi is the county with the highest population density (149.9 inhabitants/km^2).

The changes in population dynamics, the demographic and socioeconomic factors impact health.

The inequalities from the rural environment are reflected in the geriatric population's general and oral health.

The ageing process is associated with poor general health and occurrence of a variety of general chronic conditions, most of the time associated with poor oral health. Oral diseases are progressive and cumulate in complex conditions. Ageing is associated with structural and mechanical changes of dental structures, favouring the development of dental caries and periodontal disease.

Our study population is old, works in agriculture in their gardens, breeds animals or is retired, receiving support allowances. Lately these persons had socio-economic difficulties, due to the low monthly income, represented by a small agriculture pension.

In our studied group the female gender subjects were predominant.

Based on our data, we outlined the *general morbidity model* of older adults from the rural environment. In our study cardiovascular diseases and diabetes mellitus were the most frequent associated conditions, followed by rheumatic and osteo-articular diseases, obesity. Over half of study population had at least 2 general chronic diseases (58.71%).

In male gender, the general morbidity model is dominated by the cardiovascular disease, chronic digestive diseases and chronic rheumatic and osteo-articular diseases. The main risk factors for general health are: smoking, added salt and daily alcohol consumption.

A relatively close general morbidity model is being emphasized in female gender, which is dominated by the cardiovascular diseases, diabetes mellitus and chronic digestive disease, obesity and chronic rheumatic and osteo-articular diseases. The main risk factors are: added salt, daily alcohol consumption and smoking.

The general morbidity of rural old population correlates with dental diseases.

In our country *addressability to dental health services* in geriatric population is low, especially in rural areas (*Office for Disability Issues at the Department for Work and Pensions, 2014*). This state is determined by the organization and function of the dental system, the insurance state of the persons, the level of income and education (*WHO, 2016*). Rural population has a lower access to preventive and control interventions than their urban peers, the most frequent cause being the lack of financial support (*Sheiham A et al, 2000*).

Based on our data, we outlined the *oral morbidity model* of older adults from the rural environment, which is relatively different for the two genders.

In male gender, the oral morbidity model is dominated by the dental caries disease, lip and mucosal diseases, dental trauma and edentulism.

In masculine gender, the main risk factors for oral health are: dental calculus, radicular residues, poor oral hygiene and no tooth brushing.

A relatively different oral and dental morbidity model is being emphasized in female gender, which is dominated by the dental caries disease, non-carious dental disorders, periodontal diseases and edentulism.

In feminine gender, the main risk factors are: dental calculus, poor oral hygiene and no tooth brushing.

The most frequent conditions encountered in our study were dental caries, edentulism, periodontal disease, oral cancer and potential malignant conditions (*Heinisch, 2010*).

Bacterial colonization of native teeth and prosthesis due to lack of hygiene is frequents and causes a poor oral health status in the elderly.

The most common condition encountered in our older population was dental caries, which cause dental loss. The low literacy and a poor socio-economic status determines a high prevalence of tooth caries (*WHO, 2017*).

In elderly the prevalence of root caries was high, this high frequency being explained by recession of the gingiva and abrasion defects existing in the neck of the teeth.

A high prevalence of non-carious pathology is encountered in the elderly. In our rural geriatric population dental erosions are progressive, with definitive dental hard tissue loss, favored by local acidity.

Dental abrasion and aging have a tight correlation (*Untu et al, 2015*). These pathologic processes have a high prevalence in the elderly and remain untreated.

The most frequent cause of teeth loss is periodontal disease. This includes changes in the supporting structure of the teeth, gingiva, alveolar bone, cement and periodontal ligaments and is generally associated with chronic conditions (diabetes mellitus and cardiovascular diseases).

Periodontal disease is associated with general chronic conditions, most frequent with diabetes mellitus and cardiovascular diseases and determines loss of teeth.

There is a growing body of evidence that periodontal disease is linked with atherosclerosis, promoting and enhancing the formation and growing of atherosclerotic plaques (Sanchez et al., 2019; Beukers et al., 2017; Tonetti et al., 2013; Papanou et al., 2015). Therefore periodontal disease is a risk factor for atherosclerosis and cardiovascular disease (Sanchez et al., 2019).

Periodontal disease or periodontitis is characterized by chronic inflammation involving the structuires supporting the tooth and the bone, due to the host response towards the bacterial aggression of the oral cavity and dental plaque. Untreated, it conducts to tooth loss (Genco et al., 2000).

Periodontal disease is a major health problem worldwide (Sanchez et al., 2019; Petersen et al., 2000; Eke et al., 2015; Baehni et al., 2010; El Kholi et al., 2015).
Periodontitis is a frequent condition in adults, its prevalence growing with advanced age and associated comorbidities, being more frequent in men (Christopoulus et al., 2015; Sanchez et al., 2019).

The systemic inflammation induced by periodontitis triggers atherosclerotic cardiovascular disease, due to bacteria entering the blood stream and determining a host mediated response, generating atheroma appearance and progression (Tonetti et al., 2013; Sanchez et al., 2019).

Old people develop frequent xerostomia, hyposalivation and taste disturbances (Torpett et al., 2012; Demmer et al., 2013), due to their chronic medication and these side effects exacerbate periodontal disease progression (Sanchez et al., 2019).

There is still a matter of debate if periodontal disease treatment might reduce systemic inflammation and have favorable influence on atherosclerotic cardiovascular disease (Friedewald et al., 2009).

However there is expert consensus on the association of periodontitis and cardiovascular disease and the need for patients with cardiovascular disease to have curative and preventive oral health checkes (Tonetti et al., 2013; Baehni et al., 2010). For the elderly it is strongly recommended to attend regular dental care in order to reduce their cardiovascular risk (Sanchez et al., 2019).

The self-perceived oral health status, behaviors and hygienic practices of adults reflect their knowledge on the importance of the oral health and the link between periodontitis and cardiovascular disease.

The development of periodontal disease is favored by precarious oral hygiene, the poor general health and comorbidities (*WHO, 2015*).

The diseases of the temporo-mandibular joint and associated structures induce poor mastication and are frequently cause of pain and discomfort. They are also difficult to diagnose and treat.

Lack of addressability to dental care in the elderly population is caused by financial problems, difficult locomotion, negligence, fear of pain and low education level and illiteracy. The causes are the same, in both genders.

This rural population has multiple general, dental and social needs. In order to change things special health and social policies are needed. Policy makers (the Health Ministry and the Health and Social Insurance Houses) can estimate the necessary resources to implement community integrated health programmes designed for elderly in rural areas.

2.3.5 CONCLUSIONS

- Geriatric rural population has a poor general and oral health.
- General and dental health services in rural areas are deficient in number and rural population's access to them is low.
- The high morbidity revealed by our present study suggests that it is needed to develop public health services for the geriatric population from rural area of the North-Eastern region of Romania.

2.4. HEALTH EDUCATION AND HEALTH PROMOTION IN SCHOOLS

2.4.1. **INTRODUCTION**

Health Promotion in a school (HPS) setting may be defined as any activity that aims to improve and protect the health of the school community (WHO, 2017). The HPS strives to make school a positive experience for students and staff, paying special attention to all aspects of health in every area of the school (IUHPE, 2009). The whole school community takes action and places priority on creating an environment that will have the best possible impact on the health and learning of pupils, staff and parents (WHO, 2009).

Health education builds students' knowledge, skills, and positive attitudes about health. Health education teaches about physical, mental, emotional and social health (https://www.healthpromotion.ie/hp-files/docs/HPM00841.pdf). It motivates students to improve and maintain their health, prevent disease, and reduce risky behaviors.

On an international level, adolescents' health is recognized as a fundamental component of human development and welfare, on which depends the population's health, as well as the prosperity and development of all countries. In this respect, the EU Health Strategy „Health is the greatest wealth", 2008-2013, emphasizes the fact that „a good health state, from prenatal period, to adolescence constitutes in fact an important social and economic resource".

The WHO triggers in its report over „The Health Behavior of School-aged Children

(HBSC)" that in central and East-European countries, among which Romania is mentioned also, „adolescents' health is neglected by the authorities, therefore they are vulnerable and they have limited access to health services".

On national level, two strategic documents identify the main directions and major interventions in children and young people's health: „National Health Strategy 2014-2020" and „National Strategy for protection and promoting children rights for the period of 2014-2020".

2.4.2 MATERIAL AND METHODS

Our research respected the methodology of the prevalence studies.

The investigation file used for collecting data comprised the following sections: general, social and economic factors; addressability to health services; general and oral and dental morbidity; attitude towards the general and oral and dental health condition; oral and dental health, pathology and hygiene.

The study was developed following on two research directions:

1. An elaborated questionnaire in this sense (the research method being social and medical enquiry), the quality of the answers being evaluated on a Likert scale; the obtained data was statistically processed using the following indicators: frequency, structure (the percent of the present/ absent answers), central tendency for quantitative characteristics (medium value) and for testing statistical significance of differences;
2. Clinical examination of adolescents regarding general and oral and dental health collected in the database.

The data provided by the questionnaire were corroborated with the results of the clinical examination. The demographic, social and economic factors, considered independent variables, were: age (already turned), gender (male/female), parent's education and type of family. For the family income level, the following categories were established: poorness, reduced and medium.

In our study, the prevalence of the general morbidity, the indicators of oro-dental morbidity, the addressability of the adolescents from the rural environment to the general practitioner and to the dental medicine services in the last 2 years, oral hygiene, the degree of education for health, self-perception of oral and dental health (SOH) and self-perception of the general health, were considered dependent variables.

For the study of general morbidity for the adolescents from the rural environment are used the International Classification of Diseases and Health Problems, Revised Version 10 (ICD10-2013).

For the study of oral and dental morbidity the indicators recommended at European level were followed and were correlated with the prevalence of general diseases indicators.

The present study was realized with the aim of knowing the level of health education of adolescents in the rural environment, correlated with their health condition (general and oral and dental aspects). In order to reach this aim, the research set the main specific objectives:

1. To evaluate the cognitive level of health education regarding general and oral and dental health condition;
2. To assess general morbidity and oral and dental morbidity in the studied group.

The results of the study are useful for planning a health promotion program, integrated at a community level. This programme addresses the main health problems raised into question by secondary school students from the rural environment.

The group of subjects considered for this study comes from a rural community of Iasi county, located in the North-Eastern region of Romania, having 4975 inhabitants, out of which 341 (6.85%) adolescents.

2.4.3 RESULTS

Initially there were 168 adolescents included in the research. Due to the fact that the global participation rate to our study was 95.24%, in the final group remained only 160 subjects, with ages between 13 and 15. The mean age for the total studied group was 13.92 years, 13.85 years for females and 13.98 years for males.

The studied group is representative for adolescents from the rural area within Iasi County, the maximum error being ± 2.68%.

Gender distribution of adolescents included in the studied group evidenced the high prevalence of the masculine gender subjects (88 persons, respectively 55.0%) and lower of the feminine gender subjects (72 persons, respectively 45.0%).

Following a social and economic aspect, the studied group included adolescents from the rural environment whose parents either work abroad, or in their own homes doing subsistence agriculture and animal husbandry, or which beneficiate from minors' allowances.

Most of the adolescents from the studied group were from families with reduced monthly incomes, who have confronted with significant financial difficulties in the past few years.

Adolescents from the studied group filled in a health education questionnaire, which gathered questions related to health, disease prevention, personal and oral and dental hygiene.

The calculated mean value for all the answers offered by the adolescents from the studied lot to the health questionnaire is 1.86 for the total group (on a 0-4 Likert scale), 1.8 for male gender and 1.9 for female gender.

Table 2.5 shows main answers to the most important questionnaire items.

The unsatisfactory general level of the answers received for the questions can be explained by the lack of interest for health education as what the adolescents and their parents are concerned, as well as the teachers.

The addressability of the pupils from rural environment to the dentist is unsatisfactory.

The addressability, calculated for the total group, was 60.62% (97 subjects), respectively 59.09% (52 persons) for male gender and 62.50% (45 persons) for female gender subjects.

The accessibility of adolescents from the rural environment to health services is influenced by factors related to organizing and functioning of health system, parents' education, but also by the family income.

The reduced addressability to physician is a significant risk factor to the overall health of adolescents in rural areas. We noticed a significant association between parents' low education level (ISCED 1) and the reduce addressability to the family physician/pediatrician of the middle school students in rural areas (OR = 1.14).

Table 2.5 Main answers to the health education questionnaire

Age / Gender / Item:	13-15 years		
	Male n_1 (%)	**Female** n_2 (%)	**Total** N (%)
	88(55.0%)	72(45.0%)	160(100.0%)
When is it mandatory for hands to be washed:			
-unsatisfactory/ incomplete answer [1];	27(30.68)	17(23.61)	44(27.50)
-satisfactory answer [2];	21(23.86)	19(26.39)	40(25.00)
-good answer [3];	19(21.59)	23(31.94)	42(26.25)
-very good answer [4];	16(18.18)	12(16.67)	28(17.50)
-non-answer [9].	5(5.68)	1(1.39)	6(3.75)
Mean value	2.0	2.1	2.07
How are „contageous" diseases transmitted?			
-unsatisfactory/ incomplete answer [1];	22(25.00)	16(22.22)	38(23.75)
-satisfactory answer [2];	31(35.23)	27(37.50)	58(36.25)
-good answer [3];	17(19.32)	14(19.44)	31(19.37)
-very good answer [4];	13(14.77)	9(12.50)	22(13.75)
-non-answer [9].	5(5.68)	6(8.33)	11(6.87)
Mean value	1.7	1.8	1.73
Odds Ratio (OR); *CI 95%*- Confidence Interval95% for OR.			

General morbidity (Table 2.6) of secondary school students from the rural environment taken for study, dominated by untreated diseases (19.63%) and recently diagnosed (13.08%), with only 18.69% of the cases correctly diagnosed and treated determines social and health problems that are difficult to handle, on a medium term or long term.

Table 2.6 Prevalence of general morbidity, smoking and alcohol consumption

Age / *Gender* / **Factors:**	13-15 years		
	Male n_1 (%)	**Female** n_2 (%)	**Total** N (%)
	56	51	107
General prevalence	29(51.79)	26(50.98)	55(51.40)
Smoking	5(8.93)	3(5.88)	7(6.54)
Alcohol consumption	3(5.36)	1(1.96)	4(3.74)

In our study, the prevalence of smoking had a low value (6.54%) as compared to the average of urban area at national level (14.2%).

A relatively healthy lifestyle was registered for 20.32% of the subjects, being insignificant higher in the case of males than in the case of female subjects, 23.82% vs. 17.59%.

The highest number of subjects with a healthy lifestyle was registered in students with the age of 15 years (17 persons– 10.62%).

The oral and dental morbidity in the case of secondary school students from the rural environment is relatively different for the two genders.

The calculated addressability for the entire lot was 66.87% (107 subjects), respectively 63.64% (56 persons) for males and 70.83% (51 persons) for females subjects.

2.4.4 DISCUSSIONS

The school psycho-social environment includes the social environment, the interpersonal relationships in school and the way pupils and staff interactions, but also the pupils' learning experiences.

The material, social and emotional environment in which pupils spend a considerable time in a day can influence their physical, emotional and mental state, and also their wellbeing and interfere with the school dropouts. (Jamal et al., 2013).

The World Health Organization has developed the psycho-social environment profile as a tool to help teachers, parents and pupils in their effort to build a positive psycho-social climate in schools, as a way to improve the education's quality and promote physical and mental wellbeing in learners (WHO, 2000).

Because school environment is a fundamental determinant of the multiple factors influencing the education's quality, the assessment of the psycho-social environment's profile has maximal efficiency when used as an integrated part of concentrated efforts to create friendly schools and promote adolescents' wellbeing (WHO, 2000).

The World Health Organization recommends the use of the psycho-social environment profile as an integral part of the global effort to promote health through school, together with other instruments used in Local Action: Creating Health Promoting Schools, WHO/ School/00.3 (European Agency for Safety and Health at Work, 2013).

Research on rural educational environment pinpoint the existence of a strong relationship between the social environment conditions and short and long term emotional wellbeing of pupils (European Agency for Safety and Health at Work, 2013).

Taking into account the considerable time spent by pupils in school, a consistent body of research on psycho-social school aspects is developing, investigating the school's impact on health and emotional wellbeing of pupils (European Agency for Safety and Health at Work, 2013).

Periodical prophylactic medical exams are a valuable instrument for the assessment of the health status at individual and population level. This is why they are used as an important method in public health and preventive medicine. Due to their anatomic, physiologic resilience and health children and adolescents represent an important segment of an areal's population. In children and teenagers health has a more favorable situation than in adults, but it also carries specific vulnerabilities.

The health of these ages can be considered as an indicator of a collectivity's health and a prognostic item for the following ages.

The health of children and teenagers should be one of the principal motives of concern for policy makers, because ensuring health at these ages is a guaranty for an acceptable health level of the following generations (Jamal et al., 2013).

In the past few years, the concept of rural health has become more and more noticeable (Bilinski, 2010). This refers to an interdisciplinary field of public health. It deals with the study of the health level of the population coming from the rural environment, comprising several fields of study: public health, sociology, health economy, family practice, dental medicine, nursing (https://www.cdc.gov/chronicdisease/pdf/factsheets/Rural-Health-Overview-H.pdf).

According to the principle of equity in health, all citizens should have equal chances at health. In spite of this, if we are to talk about many developing countries around the world, there are significant differences between the rural and urban population as to what concerns the general and oral health.

The population from certain rural regions of EU, also in Romania, confronts with

difficulties related to accessibility to basic health services.

In Romania, the primary health services are provided by general practitioners who offer preventive and curative medical services for all children, regardless of the medical insurance that the parents/legal guardians have or do not have. The fact that in the rural environment there are fewer practitioners (general and dental practitioners), fewer medical services and the fact that there is a total lack of health education programs and programs promoting general and oro-dental health, basically means fewer preventive medical services and an increase in the response time as to what emergency situations are concerned (Rourke, 2008). So, adolescents from the rural environment generally have a reduced accessibility to health services, by comparison to that of adolescents from the urban environment.

Due to particularities related to anatomy, physiology, health and adaptability, adolescents, especially those coming from the rural environment, are an important population group, coping with specific problems and vulnerabilities (de Sante-Bertkau, 2019). Social and economic factors are affecting health; therefore, inequalities at this level are reflected in the general and oral and dental health of adolescents from the rural environment (Curtis, 2011).

The main problems that can be found when it comes to primary health care are a limited capacity of actively identifying health risks among children in rural communities and the limited offer of preventive medical services in the main health package (Miller, 2018).

Numerous research sustain that in the families where parents have a low financial status and a low educational level, children adopt an unhealthy life style (WHO, 2009).

Also, poverty has a negative impact on adolescents in the rural environment, 40% of them living in poor conditions or even at the limit of subsistence.

Poverty affects adolescents' health and development by limiting access to health services, to a correct and balanced nutrition and to education opportunities on the one hand, and on the other hand, poorness influences the teenager's family, determining the parents to leave the country in order to look for a job.

Adolescents from the rural environment represent a highly vulnerable population group that requires the implementation of a health promotion program at community level (Rew, 2014).

Adolescents' health ought to be one of the primary concerns for the decision factors, with the purpose of ensuring an acceptable health level for future generations. Emphasis is made on a coherent health politics, based on health education and health promotion (https://www.healthpromotion.ie/hp-files/docs/HPM00841.pdf) which should include:

- an efficient control of the risk factors for health, mentioning the ones that are common also for general diseases, as well as for oral health, in order to simultaneously prevent general and oral and dental diseases;
- implementing health programs designed for preadolescents and adolescents from the rural environment, coming from poor families (Faught et al, 2017);
- the technical and legislative support necessary for configuring an efficient health system, that integrates the general and oral health.

Also, partnerships between governmental authorities, educational institutions and rural communities could strengthen the health system in rural areas and tailor educational

programs for rural health practices, consequently decreasing the healthcare gap between rural and urban communities.

2.4.5 CONCLUSIONS

- Adolescents from the rural area have a precarious general and oral and dental health status.
- The unsatisfactory level of answers to the general health questionnaire can be explained by a low interest regarding health education in the adolescents, as well as their parents and teachers.
- Accessibility to health services that adolescents from the rural area have is influenced by factors related to the organization and function of the health system, but also to the family's income level and parents' education level.

2.5. THERAPEUTIC EDUCATION IN PATIENTS WITH DIABETES MELLITUS

2.5.1. INTRODUCTION

One of the most important professional tasks of physicians and nurses as well is therapeutic education of patients with chronic diseases, at each encounter with the patient. It regards not only the description of the disease, its natural evolution and possible complication, but also important data on therapy, meaning the needed life style changes and the chronic medication regimen, which can be at times a very complex one. Chronic diseases need permanent medication, so compliance and adhesion to treatment are highly important. In diabetes mellitus constant patient education is reported to enhance adherence to treatment and determine a better clinical outcome (Doupis et al, 2019). Patients should be also educated on possible side effects of those drugs and advised to contact their physicians in case they appear.

Patients' negative perceptions and beliefs about drug therapy are as frequent as other barriers (economic, social, geographic etc) to accessing treatment, but are more frequent than external factors associated with non-adherence (Gagnon et al, 2017).

Patients with diabetes mellitus require intensive therapeutic education on their pill regimens and on insulin therapy, about its action and risks, as well as preservation and the acquisition of the technical skills its administration requires.

The diagnosis of diabetes and the need for chronic insulin injections represent a consistent stress for patients, with psychic and social consequences (Hancu et al, 2008; Christie et al, 2014). Patients' negative beliefs about insulin are a main barrier to therapy adherence (Gagnon et al, 2017). First months after diagnosis are very important for the implementation of the needed life style changes. Researchers (Assal and Lacroix, 1998) described five stages of adaptation of the patient with chronic disease to the new condition. During this interval transition from shock to active phase is achieved, the patient with

diabetes accepts the illness, becomes responsible and attains emotional balance, being able of self-control and adjusts the therapy according to the changing conditions of daily life. The main purpose is to integrate the diabetic patient into daily family life and social activities. Therapeutic education has an important role in sustaining the theoretical and practical need for active involvement of the diabetic patients into self-management. This can be achieved by self-empowerment, in order to take the correct therapeutic decisions in special situations (Christie et al, 2014).

There are patients who refuse to accept that they have diabetes, while others accept the disease, but dissimulate it in the social environment, afraid that other people would judge, or reject, or change their attitude towards them.

The acceptance of a chronic disease depends on the optimal relationship between the shared responsibility of the medical care team and the patient. The diabetic patients will evolve from the passive stage to active self-involvement, becoming thus his or hers own doctor. This allows a higher level of autonomy (Tanwani, 2011).

Some studies emphasized the main barriers to insulin's treatment initiation, related to the fear of patient health's worsening, the risk of hypoglycemia and fear of needles, the social stigma and the necessity of learning at an older age (Venter N, 2006). The lack of adherence to the medical treatment fosters a negative impact on the metabolic control and increases the risk of chronic complications (Christie et al, 2014).

Therapeutic education has a very well documented role in the diabetes nursing plan (Hermanns et al., 2015). At the moment, the interdisciplinary care team receives an increasing role in patient's management. The working hypothesis of our study was the presence of a relationship between the level of patients' knowledge on insulin therapy and the barriers to its administration.

2.5.2. MATERIAL AND METHODS

The aim of the study was to assess knowledge on insulin treatment and to identify the main barriers to the correct management of insulin treatment in an elderly diabetic population.

We developed a cross-sectional study in 113 elderly diabetic in-hospital patients from the Diabetes, Nutrition and Metabolic Diseases Department in The Clinical Emergency Hospital "Saint Spiridon" Iasi, between 1-st of May 2014 to 30th of June 2015. The exclusion criteria were the existence of cognitive impairment due to neurological or psychiatric diseases. Thirteen patients refused to participate in the study or couldn't provide complete answers to the questionnaires, so the final sample included 100 diabetic patients. All patients signed the informed consent for participation in the study. We applied two questionnaires.

The first questionnaire was administered by an investigator and targeted data on demographic characteristics (age, area of residence, gender, marital status, duration of formal education), the type and duration of diabetes. The patients were invited to answer questions on their degree of autonomy regarding insulin therapy, compliance, injections' schedule, the presence of an embarrassing feeling when having to inject insulin in public and were asked to pinpoint the barriers to insulin's administration. The answers from the open question related

to barriers to insulin's administration were evaluated through thematic analyses. They were coded in order to identify and to form themes.

The second questionnaire included 27 questions that focused on insulin therapy and was completed directly by the participants, in order not to influence their answers. There were simple questions, with four alternative answers. The items took into account the specific components of education in insulin therapy (understanding the types of insulin, their duration of action, main storage conditions, insulin injection technique and specific adverse reactions). The analysis of questions consisted in determining the index of difficulty, which indicates the percentage of respondents who correctly answered the same question. Questions with a difficulty index greater than 0.8 or less than 0.2 are not recommended (Venter N, 2006). The distribution of the alternatives of responses represents the percentage of people who gave the same answer to the same question. It is recommended to take into account items in which at least 5 % of people had the same answer (Venter N, 2006). The ability of each item to discriminate between people with different levels of knowledge was measured correlating the score for each item with the overall test score, eliminating the items with a lower value than 0.2 (Venter N, 2006). Criteria for the assessment of the items 'analysis are shown in Table 2.7.

A questionnaire with 17 items resulted so, eliminating those questions which were not noted with a significant correlation compared to the total score. The questionnaire was assessed by determining the internal reliability, using Cronbach alpha coefficient, which had an acceptable value (0.77). Questionnaire score results had an average of 11.5.

Statistical analysis

The statistical analysis of data was performed with the SPSS Programme (Statistical Package for Social Sciences) version 13.0 for Windows (Chicago, IL, USA). For numerical description of variables we performed measurements of central tendency and determined the data' dispersion indicators.

The coefficients of correlation were determined in order to assess the association between variables. Nonparametric tests were used to test the differences between the mean values of two sets of scores, knowing that the data did not have a Gaussian distribution. The chi-square test ($\chi 2$) was used to compare nominal, dichotomous variables or proportions (Howitt et al, 2010).

Table 2.7. Items' analysis

	Correlation with total score	**Item difficulty**		**The distribution of alternatives**			
		Corect	Not correct	1	2	3	4
I1	.312*	80	10	2	8	90	10
I2	.213	38	62	8	14	40	38
I3	.495**	80	20	4	8	80	8

I4	.495**	70	10	80	6	30	4
I5	.200	88	12	88	4	2	6
I6	.358*	72	28	90	72	6	2
I7	.544**	58	42	58	16	12	14
I8	.082	22	78	60	22	6	12
I9	.343*	78	22	78	12	2	8
I10	.280*	64	36	64	20	4	12
I11	-.026	68	32	68	10	22	0
I12	.062	46	54	22	30	46	2
I13	.505**	68	32	12	6	68	14
I14	.205	66	34	66	12	20	0
I15	.138	80	20	16	80	2	2
I16	.614**	76	24	76	6	18	
I17	.507**	66	34	8	20	66	6
I18	.601**	70	30	14	70	10	6
I19	-.202	10	90	10	8	70	12
I20	.303*	64	36	64	12	22	2
I21	.592**	62	38	16	10	62	12
I22	.361*	62	38	38	40	12	10
I23	.382**	60	40	16	60	10	14
I24	.394**	48	52	10	48	30	12
I25	.344*	66	34	26	6	66	2
I26	-.010	14	86	14	70	2	14
I27	.071	22	78	78	22	10	10

* $p<0.05$, ** $p<0.001$

2.5.3. RESULTS

The study included a total of 100 elderly type 2 diabetic patients, with age limits between 65 to 85 years (mean age 72.68 years). The group included a total of 62 patients from urban areas and 38 patients from rural areas; 56% patients were male and 44% female. A few patients had higher education (5%). Most patients finished high school education (55%) or gymnasium (40%). The mean duration of diabetes was 6.79 years. Although most patients said that they administered the insulin with a constant schedule (54%), there were 40 patients who declared that sometimes they delayed injecting the insulin, whereas 6% had often delayed to administer the insulin. In our study, 22% patients said that it happened to them to forget to inject the insulin and 4% interrupted insulin's administration for a longer

period. In our study 16% of patients felt embarrassed when they had to inject insulin in public.

Patients who declared that they always injected the insulin at the same time had a lower average knowledge (as revealed by the questionnaire) compared with those who said that sometimes or often they delayed to inject the insulin with a constant schedule, but the differences were not significant (p=0.234). Patients who said they happened to forget to manage their treatment had a lower average knowledge in managing insulin treatment (p=0.369). Patients who said they felt embarrassed to inject insulin in public had a lower level of knowledge (p=0.04) (Table 2.8).

Table 2.8. Adherence to insulin therapy plan and the score on knowledge questionnaire

	Score	**N**	**Mean**	**Std. Deviation**	**95% Confidence Interval for Mean**	
Respecting insulin schedule	Always	54	10.70	3.01	9.51	11.89
	Frequent	40	12.40	4.27	10.40	14.39
	Sometime	6	12.66	1.52	8.87	16.46
Temporary voluntary interruption of insulin therapy	No	78	11.25	3.63	10.07	12.43
	Yes	22	12.36	3.32	10.13	14.59
Embarrassment in insulin administration in public	Yes	84	11.95	3.59	10.66	12.90
	No	16	10.00	3.25	7.28	12.71

The most important barriers to insulin treatment were: frequent blood glucose tests, the need to respect the schedule or diet, associated fear of needles or bites. Although most patients did not report complaints related to treatment, 16% of them declared they feared the bite related to insulin injection or related to blood glucose test (32%) or to schedule a very strict diet. Results are presented in Table 2.9.

Tabel 2.9. Complaints related to insulin treatment

The most important complaint related to actual treatment	%
No complaint related to actual treatment	40.0
Complaints related to frequent blood tests	14.0
Very strict insulin schedule or diet	14.0
Fear of needles or bites	16.0
Medical system	16.0

There were significant differences in scores achieved by respondents and complaints related to current treatment (Table 2.10).. Patients who did not report complaints related to treatment and those who had as main complaint the need to respect the schedule of insulin

had a lower level of knowledge (p=0.01). Patients who had as main complaint the need of frequent blood sugar testing had a higher level of knowledge than those who had problems with the injections' schedule (p=0.02).

Table 2.10. Complaints related to treatment and questionnaire score

Score	N	Mean	Std. Deviation	Std. Error	95% Mean Confidence Interval	
No complaints related to treatment	40	11.15	3.28	.73	9.61	12.68
Frequent blood glucose testing	14	13.85	4.45	1.68	9.74	17.97
The need of very strict diet	14	10.14	3.57	1.35	6.83	13.45
Fear of bites or needles	16	11.62	3.02	1.06	9.09	14.15
Medical system	16	11.37	3.88	1.37	8.12	14.62

2.5.4. DISCUSSIONS

Therapeutic education is considered as an important intervention which could shape the attitudes and behavior towards a healthy lifestyle. One of the main objectives of World Health Organization (WHO) published in the Report is to alert all healthcare providers regarding primary prevention and lifestyle intervention (WHO, 2004). In "WHO/ The World Health Report Reducing Risks, Promoting Healthy Life" published in 2002, the necessity of government and community organizations interventions to promote the decisions to promote a healthy lifestyle is highlighted (WHO, 2002).

Therapeutic education and its evaluation should have their cornerstone on a well-documented theoretical framework. A theory has been defined as a "a plausible story that makes narrative or causal sense out of a series of phenomena." (Ryan A, 1970). Among the qualities of a theory are the ability to explain what happens during diabetes patient education and to be so explicit to be understood by other professional involved in the process of teaching. On a different note, a theory should explain the way things are, but not why they are in that way or how they are in that manner. This goal is based on the coherence of the ideas and paradigms included. This starts with the description of the observations on the studied phenomena. If someone can explain through multiple observations the occurrences of the differences and their directions, it also could constitute a descriptive theory.

Another quality of a theory is to explain why the things are in a certain way, in other words to explain different levels of knowledge through standardized questionnaires. These sort of questionnaires are able to answer questions about the efficiency and justification of a certain educational program and also can compare different programs with the same goal in the field of diabetic education. This aim refers to the ability to predict the same changes in different settings and educational programs. Also a theory should be the foundation for the ability of an education program to influence the participants to realize a better outcome in self-management of diabetes.

Health related choices are influenced by people's beliefs and their susceptibility to specific aspects of a disease, such as treatment, complications, self-management, life style changes, ability to cope and to self-care. These aspects are explained by ***the Health Belief Model*** (Anderson RM, 2005).

Trans-theoretical Model of Change helps to understand the role of the motivation on certain patterns of self-care and attitudes regarding health. The individual behavior is achieved through a process that has six stages, each of them characterised by certain attitudes and behaviors. The stages described by the transtheoretical model of change are precontemplation, contemplation, determination, action, maintenance and termination of change. The process of achieving the stages of behavior changes is called decisional balance, which consists in subjective appreciation of benefits and costs, but also the arguments for and against change. Thus, the benefits include emotional, social or health achievement, and the costs can be represented by obstacles such as social pressure, dependence on a certain vicious habit or even the desire to continue the current behavior. The trans-theoretical model makes a clear distinction between the stages of contemplation and preparation, and that of overt action. The health belief model proposes that three constellations of factors are associated with the likelihood of change at the individual level: socioenvironmental and demographic factors, the individual's perception of the threat of disease, and the individual's perception of the potential value of treatment. If all these factors point in the direction of favorably perceiving change, a person is considered "predisposed to action," or intending to act (Prochaska JO, 1982).

The evaluation of the stage in which the individual is in allows the choice of an appropriate educational intervention. The trans-theoretical model allows the trainer to provide the individual with the appropriate intervention, as part of a health education program, depending on the stage of changing the behavior in which the individual is. At each stage, the primary goal of the educator is to encourage the individual to identify the benefits of the change process and to overcome obstacles that may hinder behavior change. In this way, the educator can support the individual to tilt the decision-making balance in favor of changing behavior (Prochaska JO, 1992).

Theory of Reasoned Action starts from the assumption that exposing individuals to new information, increases the baggage of knowledge about healthy lifestyle and influences the choices regarding health. Instrumentality is determined by three things: their attitude toward the specific behavior, their subjective norms, and their perceived behavioral control. The more favorable the attitude and the subjective norms and the greater the perceived control, the stronger the person's intention to perform the behavior. Intention towards a behavior is shaped by the person's attitudes and expectancies of social environment, which act as pros and cons towards a behavior (Clark NM, 2009).

The Theory of Planned Behavior presents an additional variable, perceived behavioral control, which reflects the fact that factors external to personal control, such as social support, income, time or various opportunities, can affect the individual's intention and behavior. Essentially, the theory of planned behavior emphasizes that an individual will adopt a type of behavior when he considers that the benefits of success are greater than those of failure, and individuals around him will consider that practicing the new behavior will benefit him. Successful application of the new behavior will be the final result, if the individual has

sufficient control over external or internal factors that could influence its adoption (Ajzen I, 1994).

Social representations constitute the social environment as ideas and unquestioned realities, though they have a dynamic nature, "What is most striking to the contemporary observer is their mobile and circulating character; in short, their plasticity. We see them, more, as dynamic structures, operating on an assembly of relations and of behaviors which appear, and disappear, together with those of the representations." (Moscovici,1984, p.18). Social representations are important for understanding social change as it is through representations that the behavior of individuals is influenced. Patients with diabetes usually have a diverse set of illness beliefs that do not fit the medical view of diabetes. These beliefs are determinants of patients' emotional well-being and self-care behavior. Individuals often have relatives or know people who have diabetes, have seen media portrayals of people with diabetes, and have heard about some of the complications of diabetes. Therefore, individuals come to the workshops already having a social representation of diabetes, even if these beliefs are not necessarily accurate, up-to-date, or complete.

Self-Regulation Theory focuses on individuals' illness representation or personal model of diabetes as a key determinant of their behavioral and emotional responses to illness. In this case, illness representation is formed by four core elements identity (What is diabetes? What symptoms are experienced? What is actually wrong?), cause (What caused my diabetes?), timeline (How long will this last?), consequences (How will diabetes affect me now and in the future?) and treatment effectiveness (How good is my treatment at controlling or curing my diabetes?) (Skinner T, 2003).

The social position of elderly depends on the ethnic and cultural context. Elderly people are considered a socially disadvantaged group in the modern industrial society. The eight stages of human life are marked by one major objective, whose achievement ensures the integrity of ego. Failure to achieve this goal generates despair. Integrity of ego is linked to self-acceptance, lifestyle and belief that previous decisions were the best for the specific conditions of that time. Despair is a mental attitude and condition, opposed to dissatisfaction and disappointment, due to belief that decisions were not optimal (Erickson, 1968). Havighurst (1972) defines the human behavior through the stages of personal development objectives. Their achievement builds the satisfaction feeling.

Diabetes self-management education (DSME) can be delivered in different manners. One of these is "one size fits all," in which programs are designed for a large group of individuals. It doesn't take into account individual needs of the participations or differences determined by the stage of the disease or the association with other comorbidities. One the other hand, there are the so called tailored programs, which adapt their curricula according to the individual necessities of the participants. The second involves "tailored" programs, which are modified for the needs of each individual. This approach is effective at changing behavior, but their cost-efficiency is debatable. Therefore, many diabetes educational programs incorporates the approach "one size fits all," a group-based approach originally designed for the majority of patients. Programs need to address the variations in cultural values underlying motivations, preferences, and behaviors of individuals from different ethnic groups by using approaches that are adapted both to the targeted group and to the individuals within it (Osborn CY, 2008).

The personal goals of the third age are: accepting and adapting to decreased physical force and impaired health, retirement and reduced income, to the death of close people and achieving satisfactory arrangements for the physical life. The following concepts are desirable personal goals for the elderly: maintaining a sense of self-esteem, solving old personal conflicts, adapting to the death of close people and environmental changes (Parmenter et al, 1999). Low adherence in elderly diabetic patients to insulin therapy is determined by the psychological or cognitive capacity to adapt to new life conditions.

One of the major goals of treatment of type 2 diabetes is to prevent chronic complications. Low adherence to treatment in elderly patients is determined by a lot of psychological, cognitive or emotional factors and the ability to adapt to new life conditions (Palos R. et al, 2007).

In our study, the adherence to treatment was assessed from two viewpoints: the congruence with the indication of the number of daily doses of insulin and the schedule of insulin. In our study, most patients declared that they administered the insulin with the same daily schedule (54%) and 22 % of patients said that they sometimes forgot to inject their insulin.

Taking into account that the average duration of a diabetic patient's examination in the office is about 5-7 minutes, it is useful to assess the therapeutic knowledge and insulin-related barriers to a correct treatment (Ionescu-Targoviste, 1997). Better adherence requires the need for a more intensive therapeutic education in this population, especially in elderly with low skills in insulin's injections. Main complaints regarding insulin treatment in elderly diabetic patients are: frequent blood glucose testing, the strictness of the treatment, the need to follow the schedule or diet, fear of injections and barriers linked to the medical system (Abaterusso et al., 2008).

There are authors (Peyrot et al., 2010) who emphasize that some patients tend to omit one to two injections a day, sometimes intentionally, skipping to inform their physician or hindering that fact. Therefore, the medical team needs to identify these patients and imagine strategies to ensure both good diabetes control and minimal changes of the daily schedule (Tong et al, 2015). A big challenge is to perform continuous glucose monitoring (using Continuous Glucose Monitoring System). The emotional factors related to patients' perception may adversely affect the results, being related to the displeasure of wearing the device for 3-5 days, the painful sensations and the high cost of sensors (Tong et al, 2014).

The optimal timing of initiation of the insulin therapy appears to depend more on the level of patients' perception than on the assessment of therapeutic knowledge, injection skills or insulin's structure (Christie et al, 2014; Abu Hassan et al, 2014; Lee. et al, 2014).

2.5.6. CONCLUSIONS

- Cognitive factors' improvement could help them surpass the emotional barrier entailed by the fear of daily injections, lifestyle and attitude changes towards diabetic chronic complications.

2.6 DIAGNOSTIC MARKERS IN ACUTE INFECTIOUS COMPLICATIONS OF DIABETES MELLITUS

2.6.1. INTRODUCTION

Previous studies have reported that diabetic patients are more susceptible to infection than non-diabetic patients. It was estimated that 10% of emergency room visits among diabetic patients were attributed to different types of infections (osteomyelitis, pyelonephritis, cystitis, pneumonia, cellulitis, sepsis and peritonitis) and they were more prevalent in people with poor blood glucose control (Wang et al, 2019).

Sepsis represents a systemic inflammatory response syndrome caused by severe infection. Systemic inflammatory response syndrome (SIRS) represents a clinical expression of the host response to inflammation (Zhou et al, 2014; Levy et al, 2004). A recent study of a cohort derived from the Healthcare Cost and Utilization Project's National Readmission Data from 2013 to 2014 identified diabetes as a predictor of 30-day readmission (Grade SK. Et al, 2019). It is considered that diabetes is more often associated with infection and a poor prognosis because hyperglycemia impairs the functionality of neutrophils, the functions of macrophages and the bactericidal activity of leukocytes (Gomesa.et al, 2017; Trevelin.et al, 2017). However, the mortality rate of septic patients with diabetes mellitus (DM) was slightly lower than that of non-diabetic patients in a recent meta-analysis of 10 studies performed between 2000 and 2016 (Wang et al, 2017). A recent retrospective study using Multiparameter Intelligent Monitoring in Intensive Care III database, concluded that type 2 DM does not increase mortality in intensive care units (ICU) patients with sepsis secondary to bacterial pneumonia and also that the mean glucose levels during the hospital stay positively correlated with mortality in non-DM patients but not in type 2 diabetics (Sathananthan M. et al, 2019). Another retrospective large database review found that diabetes was not associated with 90-day mortality risk in critically ill patients admitted with sepsis (van Vught et al, 2017).

Detection of new diagnostic biomarkers in patients with sepsis is aimed to improve their prognosis. Although the "gold standard" for diagnosis is considered bacterial culture, it was not associated with the prognosis of sepsis and has some limitations. C-reactive protein, white blood count and neutrophil percent are traditional indicators of inflammation and infection (Wang et al, 2019).

Procalcitonin (PCT), which is normally secreted by thyroidal parafollicular C-cells under normal conditions, is ectopically secreted during infection into the peripheral bloodstream by peripheral blood monocytes and macrophages. It increases rapidly as bacterial infection advances and is considered as a sensitive marker in patients with sepsis (Wang et al, 2019).

Presepsin is a circulating soluble form of CD14 subtype (sCD14-ST) which discriminates between systemic bacterial and nonbacterial infectious diseases (Dellinger et al, 2008). It is considered an early predictor of host response and mortality in septic patients (Kaukonen et al, 2015).

The criteria of Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) are currently used in clinical practice (Gadre et al, 2019).The most used prognostic scoring models include the Simplified Acute Physiologic Score II (SAPS II), Acute

Physiology and Chronic Health Evaluation II (APACHE II), and the newly developed SAPS III (Masson et al, 2015) and Sequential Organ Failure Assessment (SOFA) score (Cillóniz et al, 2019).

The aim of the study entitled "Presepsin as a Biomarker for Sepsis Evolutions in Diabetic Patients" was to establish the correlations between presepsin value and the prognosis of diabetic patients with sepsis. The study group included a total of 60 patients, consecutively hospitalized in the Clinic of Diabetes, Nutrition and Metabolic Diseases in 1 year, with diagnosis of sepsis.

2.6.2. **MATERIAL AND METHODS**

The quick method for presepsine determination uses a chemiluminescent enzyme immunoassay of EDTA plasma. Sepsis was defined as a suspected infection accompanied by systemic inflammatory response syndrome (at least 2 criteria: fever / hypothermia, tachycardia, tachypnea, leukocytosis / leukopenia). The evaluation of patient outcomes was assessed by calculating the SAPS II score (Simplified Acute Physiology Score) in the first 24 hours of hospitalization.

2.6.3. **RESULTS**

Sepsis was defined as a suspected infection accompanied by systemic inflammatory response syndrome (at least 2 criteria: fever / hypothermia, tachycardia, tachypnea, leukocytosis/ leukopenia).

Fever was present in 54.3 % of patients. 25.8 % of patients with sepsis had multisystem organ syndrome (MSOF). The evaluation of patient outcomes was assessed by calculating the SAPS II score (Simplified Acute Physiology Score) in the first 24 hours of hospitalization.The mean duration of diabetes was 12.68 ± 8.76 years. Diabetic keto-acidosis was associated to sepsis in 32,3% of patients. Regarding chronic complications they were present in the following proportions: sensorimotor neuropathy - 26% , autonomic neuropathy - 16.12 %, diabetic retinopathy - 45.16 % and diabetic nephropathy - 32.25 %.

In our study, mortality rate was 32,3%. There were semnificative correlations between mortality rate and SAPS II score (p = 0,001), presepsine (p = 0,001), and fibrinogen value (p = 0,048). There were no semnificative correlations between age, sex, keto-acidosis, another inflammatory markers: leucocites, neutrophiles, hemoglobine, C-reactive Protein (CRP),Eritocyte Sedimentation Rate), glycemia, HbA1c and mortality rate in these patients. There were significant correlations between SAPS score, PMN value ($r = 0.6112$, $p = 0.015$) and presepsine value ($r = 0.65$, $p = 0.009$) (table 2.11).

In our study, no significant differences were observed in SAPS score in patients with chronic complications and patients without chronic complications of diabetes, except in patients with diabetic nephropathy($p = 0.009$) . SAPS score II differed significantly from those with chronic kidney disease ($p = 0.009$) or acute renal failure ($p = 0.009$) and patients without renal complications.(table 2.12).

Table 2.11. Correlations between SAPSii score and main biological parameters

Variables	**SAPSii score**
White blood cells	0,6112 p= 0,015
Neutrophils	0,3182 p= 2,48
Hemoglobin	-,2669 p= ,346
Fibrinogen	-,0061 p= ,161
HbA1c	,3810 p= ,161
Glycemia	,2439 p= ,381
Diabetes duration	0,0095 p= ,973
Heart rate	,3057 p= ,268
Lactate	,1153 p= ,0682
Predicted mortality	,9883 p= ,000
CRP	,1884 p= ,501
Co-morbidities score	,4250 p= 114
Presepsin	,6509 p= 0,009

Table 2.12. SAPS score II in patients with/without nephropathy

Effect	**Descriptive statistics**						
	Level of factor	**N**	**SAPSii Mean**	**SAPSii Std. Dev.**	**SAPSii Std. Err**	**SAPSii -95,00%**	**SAPSii +95,00%**
Total		31	40.35484	18.00287	3.233410	33.75133	46.95834
Nephropathy	yes	10	52.10000	14.48716	4.581242	41.73651	62.46349
Nephropathy	no	21	34.76190	17.02617	3.715415	27.01168	42.51212

Patients with MSOF had a higher SAPS score (p=0,001) (table2.13).

Table 2.13. SAPS score II in patients with/without multiple systemic organ failure (MSOF)

Effect	**Descriptive statistics**						
	Level of factor	**N**	**SAPSii Mean**	**SAPSii Std. Dev.**	**SAPSii Std. Err.**	**SAPSii -95,00%**	**SAPSii +95,00%**
Total		31	40,35484	18,00287	3.233410	33.75133	46.95834
MSOF	Yes	8	58.50000	12.88410	4.555217	47.72862	69.27138
MSOF	No	23	34.04348	15.09208	3.146915	27.51718	40.56978

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2.6.4. **DISCUTIONS**

Sepsis is defined by the Third International Consensus Definitions for Sepsis and Septic Shock Report as a life-threatening organ dysfunction determined by an abnormal host response to an infection. Sepsis is a major cause of in-hospital mortality. Septic shock is defined as sepsis associated with profound circulatory, cellular, and metabolic abnormalities. Patients with septic shock have serum lactate levels >2 mmol/L (>18 mg/dL) and require vasopressors to maintain a mean arterial pressure of 65 mmHg or greater in the absence of hypovolemia. The mortality rate increases according to the severity of sepsis, and gets to more than 50% mortality in severe sepsis (Angus et al., 2001). Early identification of these high-risk patients is therefore crucial Dellinger and colleagues (Dellinger et al., 2013), in the Early-Goal Directed Therapy in 2013 Guidelines of the Surviving Sepsis Campaign, recommended that a potential infection source should be confirmed as promptly as possible within the first 6 hours of presentation and that broad-spectrum antibiotic treatment must be administered within 1 hour after the recognition of severe sepsis and septic shock..

Diabetes causes a functional immune deficiency and a diminished bactericidal clearance, which explain the increased number of infectious complications and a higher sepsis mortality. (Frydrych, Fattahi, 2017). Some studies have detected a deficiency of the immunity, in diabetics, in C4 component of complement system, which is probably associated with leucocyte dysfunction and reduced cytokine response (Flyvbjerg et al, 2010). Glycation of immunoglobulin occurs in patients with diabetes in the same amount with that of HbA1c (Casqueiro et al., 2012). This may be harmful for the biological function of the antibodies (Kovach et al., 2012). Infection is one of the main causes of life threatening acute metabolic emergencies, the most severe beeing diabetic ketoacidosis (DKA) (Pelte et al., 2009).

An early marker of different infections is presepsin. It is a fraction of the soluble form of CD14 subtype (sCD14-ST). CD14 belongs to the Toll-like receptor family (TLR), which plays a role in identifying different ligands of both Gram-positive and Gram-negative bacteria and stimulates the inflammatory response (Galliera et al., 2020). Arai et al. reported that monocytes were the main source of P-SEP in humans (Arai et al., 2005) and showed that P-

SEP production was triggered by bacterial phagocytosis or a phagocytic stimulus, rather than an inflammatory stimulus.

Diabetic ketoacidosis (DKA) is a complex metabolic emergency characterized by hyperglycemia, metabolic acidosis and ketosis. Hepatic gluconeogenesis and glycogenolysis secondary to insulin deficiency, as well as the increase of counter-regulatory hormone raise the glucose level in blood and conduct to severe hyperglycemia. Lipolysis of triglycerides from fatty tissue increases serum free fatty acids. Triglycerides are lipid fractions, formed by glycerol and molecules of fatty acid. The triglycerides' fatty acids are usually different and have a carboxyl group (-COOH). The chain lengths of the fatty acids in naturally occurring triglycerides vary, but most contain 16, 18 or 20 carbon atoms. Hepatic metabolism of free fatty acids results in accumulation of ketone bodies: acetone (C_3H_6O), beta-hydroxybutyrate ($CH_3CH(OH)CH_2CO_2H$), and acetoacetate ($C_4H_5O_3$). When the accumulated ketones exceed the body's capacity to extract them, they overflow into urine, thus resulting the presence of ketones in the urine. In the absence of adequate treatment the accumulation of ketone bodies and fatty acids determines acidosis (ie, ketoacidosis), with a significant drop in pH and bicarbonate serum levels (Majumdar et al., 2010). In diabetic patients, infection represents an important stress which induces an increased level of catecholamines and cortisol.

There are some studies that emphasized that during stress or infection, less mature neutrophil forms enter in circulation. Park et al demonstrated that the proportion of immature granulocytes in circulating blood, correlated with disease severity of sepsis in critically ill patients admitted in Intensive Care Unit (Masson et al., 2015). There is suggested that incorporating the immature granulocyte assay into the routine algorithms may improve the early detection of severe sepsis or septic shock (Nagata et al., 2015). Another studies demonstrated that neutrophils from septic patients may exert dramatic compromise of endothelial barrier integrity and the effect of septic neutrophils on the endothelium depends upon the initial inflammatory event, correlating with organ dysfunction (Nakamura et al., 2014).

In some studies (Behnes et al., 2014), presepsin levels were markedly high in patients receiving HD, similar to those seen in patients with severe sepsis or septic shock. In patients who were not receiving hemodialysis, presepsin levels increased and glomerular filtration rate decreased. Some authors (Nagata et al., 2015) reported that presepsin levels significantly correlated with serum creatinine levels and the number of days on renal replacement therapy. In a retrospective study (Nakamura et al., 2014) researchers found that that presepsin levels were markedly high in patients with renal failure and end-stage kidney disease. Masson et al. (2015) reported that higher serum creatinine was the strongest determinant of presepsin levels in Intensive Care Units patients. The evaluation of presepsin levels in patients with chronic kidney disease requires further consideration.

Koizumi et al. (2017) showed that plasma presepsin level was strongly associated with the CRP level but not with the absolute WBC count, absolute neutrophil count, and absolute monocyte count. A significant relationship between white blood cells and presepsin was found, but the association with neutrophil count wasn't present in our study.

In this study, we found an important relationship between the severity of sepsis, evaluated through SAPSii score and presepsin. A study conducted recently (Bamba et al., 2018) revealed a strong correlation between the presepsin levels and the SOFA scores in 11

patients with fungal bloodstream infections. The pathophysiological mechanism which could explain this association is the increase in fungal bloodstream infections by means of phagocytosis and that this increase reflects the severity of the disease, similar to the observation in bacterial infections. A study (Liu et al., 2013) that included 859 patient admitted in ICU showed that the median levels of plasma presepsin on admission increased with sepsis severity. The levels of plasma Presepsin were positively correlated with procalcitonin, Mortality in Emergency Department Sepsis score (MEDS) and Acute Physiology and Chronic Health Evaluation II score (APACHE II) in every septic group. In this study, conducted by Liu (Liu et al., 2013), presepsin demonstrated high sensitivity (85.7%) and high negative predictive value (96.3%) in predicting septic shock, and plasma presepsin levels lower than the above-mentioned cutoff value (550 pg/ml) may help rule out the possibility of septic shock. Besides, in the logistic regression analysis, presepsin and procalcitonin were found to be independent predictors of septic shock in septic patients, which emphasises the potential predictive role of these biomarkers in sepsis. The area under the curve (AUC) of presepsin for predicting 28-day mortality in septic patients pointed out the the association with MEDS score and APACHE II score. Plasma presepsin levels in septic patients were significantly higher in non-survivors than in survivors at 28 days' follow-up. Presepsin, MEDS score and APACHE II score were found to be independent predictors of severe sepsis, septic shock and 28-day mortality in septic patients. We also found an important association between presepsin, multiple organ failure, and mortality in the patients with diabetes and sepsis.

2.6.5. **CONCLUSION**

Our study demonstrated that presepsin level is positively related to mortality rate and SAPS II score and may be considered an important serum biomarker for early detection of sepsis. According with our findings early identification of high risk patients with sepsis and diabetes is important in order to decrease the life-threatening complications associated with severe sepsis and the mortality rate. Using a panel of biochemical markers, including presepsin, would make this outcome better and easier to be fulfilled.

CHAPTER 3 - EXPERT OPINION ON RESPIRATORY THERAPY

In chronic respiratory diseases such as asthma or COPD the therapeutic approach is constantly shaped based on the results of clinical trials investigating new therapies (Highley. et al, 2019; GINA, 2019; GOLD, 2019).

Such therapies are designed to target various pathogenic pathways which are continuously detected enabling us not only to better understand the development and the progression of such diseases but also to predict their potential therapeutic effects based on their pharmacological therapies.

In asthma and COPD inhalatory therapies are most likely to be developed in order to reduce systemic exposure and hence the occurrence of side effects and in order to treat locally the pathogenic pathways mentioned above (GINA, 2019; GOLD, 2019)..

The two main areas of development of inhalator therapies in asthma and in COPD are represented by the bronchodilators and by the corticosteroids.

Inhaled bronchodilators have been the therapeutic mainstay in both asthma and COPD, bronchospasm being recognized as the underlying cause of respiratory chronic symptoms represented by dyspnea and cough and secondarily as an explanation for the effort intolerance, hyperdynamic inflation and other features of the disease.

In asthma the bronchodilators the most commonly used are represented by the beta-2 agonists. They can be given as short-acting formulation able to relieve the on acute basis the bronchospasm during asthma attacks or as long-acting formulation able to exert a more sustained effect and being indicated to be given on regular basis. However the latter types of bronchodilators are not always able to adequately reduce the symptoms and improve the lung function, especially in patients with asthma who smoke or in patients with a longer duration of disease. In such patients the other class of bronchodilators represented by antimuscarinics can be useful. This is the case especially with long-acting antimuscarinics such as tiotropium bromide, which is an inhaled therapy used conventionally in COPD but which more recently demonstrated its ability to improve disease control in asthma.

Inhaled corticosteroids are very effective in asthma and marginally efficacious in COPD, in the latter disease their use being more and more restricted due to limited efficacy. The current disease phenotypes in which such therapy is beneficial are represented by the one with eosinophilia or the one with frequent exacerbations. In such phenotypes inhaled corticosteroids are not given as a stand-alone therapy but always combined with long-acting beta 2 agonists in order to maximize their efficacy(Highley et al, 2019)..

More recently this combination was extended to a triple combination by adding long acting anti muscarinics. Such a triple combination dosed with a single device once or twice daily has the potential to improve the disease outcome not only as a result of the pharmacological effects of the components but also as a result of improved patient adherence to therapy, due to reduction of the number of inhalator devices needed to be used on daily basis (Highley et al, 2019)..

However, the available clinical trials demonstrated that in both asthma and COPD the efficacy of such inhaled therapies was not uniform and that there were subsets of patients in

whom such medications exerted a maximal therapeutic effect and others in whom the efficacy of such therapies was rather marginal. Post-hoc analysis of efficacy data allows us to identify the predictors of these two types of therapeutic responses and consequently to use these results in a more personalized approach of therapies with expected more sustained long-term effects in patients with asthma or COPD.

Sometimes the analysis of various variables of poor therapeutic response to a certain inhalator therapy yields surprising demonstration of a new pathogenic pathway on which the tested medication is rather unable to act and this is one of the reasons for the lack of efficacy of that medication. Sometimes the analysis stops at this stage and for the management guidelines of the disease only the predictors for therapeutic effects are taken forward. Fortunately, often the discovery of a new pathogenic pathway is soon followed by the identification of potential therapeutic targets of that pathway and then by the testing of various compounds able to significantly interfere with it.

In asthma and in COPD this is the case with many specific inflammatory pathways which have been constantly identified among them IL-13 driven one or TNF-α driven. Therapies able to inhibit them were generically named biological and have been investigated in many studies over the last decade (Gauvreau, 2011).

IL-13 is a cytokine which was demonstrated to be up regulated in asthma especially in patients with heavy airways inflammation and also exhibiting clinically uncontrolled or poorly controlled forms of the disease. In such patients the burden of the disease is so high and the therapeutic possibilities rather limited in terms of efficacy and of range to be used, that the identification of an upregulated cytokine-related pathogenic pathway enables the clinician to tackle it specifically with a blocking medication. This not only results in the improved disease outcome but can also be associated with a lower or no exposure to systemic steroids, which in severe asthma are given on chronic, regular basis with the increased risks for diabetes, hypertension or osteoporosis.

TNF-α was more recently found to be an important player for the chronic inflammation of the airways in patients with asthma and COPD. This inflammation cytokine was previously documented as a therapeutic target in many autoimmune diseases such as rheumatoid arthritis or psoriasis and this finding triggered the development of medications able to inhibit it which were classified as “biologic” therapies. The fact that COPD was found to improve in patients taking biological therapies for rheumatoid arthritis and having this respiratory disease as comorbidity, prompted the evaluation of such therapies in this disease.

Lung cancer is apart from asthma and COPD a prevalent condition which can be considered as being chronic. Lung cancer has specific indications for pharmacological therapy which nowadays does not only include the cytotoxic agents but also biological therapies which can be added to the conventional chemotherapy in order to enhance its tumoricidal effect. Immunotherapy is the most recent such example with nivolumab being the first check point inhibitory agent showing promising efficacy in patients with more advanced non-small cell cancer types with disease progression under conventional platinum-based regimens. In such patients nivolumab was able to improve survival, reduce disease progression and improve quality of life, with a concomitant reduction of systemic toxicity.

My interest in the domain of respiratory therapeutics is reflected by the following 5 expert opinion articles:

- **ANTOHE I,** Croitoru R, Antoniu S. Tralokinumamb for uncontrolled asthma. Expert Opinion on Biologic Therapy. 2013 Feb; 13(2):323-6.
- Antoniu SA., **ANTOHE I**. Evaluation of inhaled tiotropium in asthma, uncontrolled with standard combination therapy. Expert Opinon on Pharmacotherapy, 2013; 14(7):967-9
- **ANTOHE I**, Antoniu S, Gavrilovici C. Triple fixed inhaled therapy in frequent chronic obstructive pulmonary disease exacerbators: potential advantages for various degrees of airways obstruction. Expert Opinion on Pharmacotherapy, 2017, https://doi.org/10.1080/14656566.2017.1419186
- Alexa I, Alexa-Stratulat T, Antoniu S, ANTOHE I, Arghir O, Grigorescu C. Roflumilast in patients with advanced pulmonary disease: towards a better targeted use. Expert Opinion on Pharmacotherapy, 2018, https://doi.org/10.1080/1465566,2018.1544344
- Ulmeanu R, **ANTOHE I,** Anisie E, Antoniu S. Nivolumab for advanced non-small cell lung cancer: an evaluation of a phase III study". Expert Review of Anticancer Therapy, 2016,16 (2)165-7 DOI: 10.1586/14737140.2016.1127760;

3.2. **BIOLOGIC THERAPY IN SEVERE ASTHMA**

3.2.1. HALMARKS

Asthma is a common respiratory disease and patients with acute and poorly controlled symptoms continue to be a challenge. It is a chronic disorder of the airways in which variable and recurrent inflammation and bronchial hyper responsiveness induces bronchoconstriction (Highley. et al, 2019).

Asthma's prevalence varies from 5% to 12% of the population, accounting for over 450,000 admittances and approximately 2 million emergency visits in USA. It is more frequent in children than adults (10% versus 5%), appearing in early childhood, before 5 years of age (Morris et al, 2019).

Mortality rate is 20 per 1 million persons in USA.

The American Asthma Education and Prevention Programme (NAEPP) guidelines define bronchial asthma as a chronic inflammatory disease of the airways, in which many cells and cellular elements play role (eozinophiles, T lymphocites, neutrophiles, macrophages, epithelial cells. The inflammation, in susceptible individuals, induces recurrent episodes of cough (especially at night or during the early morning), wheezing and dyspnea, associated with different degrees of bronchial airflow obstruction. These episodes solve spontaneously or under treatment.

In recent years a better understanding of the complex physiopathology of asthma has led to progress in the therapeutic approach. The main components of the subsiding

mechanisms are airways inflammation, intermittent airway obstruction and bronchial hyperresponsiviness (Gauvreau, 2011)..

Airways inflammation can be acute, subacute or chronic. Airways edema and mucus overproduction can deepen airways obstruction and aggravate bronchial hyperresponsiviness. Infiltration of the bronchial mucosa with mononuclear cells and eosinophils, epithelial descuamation, mucus hypersecretion, smooth muscle hypertrophy and airway remodeling play an important role in asthma's pathogeny. The main cells that contribute to airway's inflammation through cytokines production include mast cells, eosinophiles, macrophages, epithelial cells, activated Th cells. Adhesion molecules (integrines and selectines), fibroblasts, epithelial and endothelial cells play role in the chronicity of inflammation. Cell derived molecules modulate smooth muscle cells tonicity and contribute to airway remodelling.

Bronchial hyperresponsiviness can be triggered by physical stimuli or cell products liberated by mast cells or nonmyelinated sensory cholinergic neurons. It is associated with increased chymase-positive mast cells in the airway's mucosa and PG D2 levels and correlates with a greater severity of the disease.

Chronic inflammation of the airways is associated with wheezing, dyspnea and cough after allergen exposure, viruses, external irritants or physical exercise. Airway's remodeling consists in smooth muscles hypertrophia and hyperplasia, angiogenesis and subepithelial fibrosis and is responsible of the partial reversibility of airflow's obstruction in chronic asthma.

Loss of balance between Th lymphocytes' populations contributes to the inflammatory process in the airways. Lymphocytes Th1 produce IL-2 and IFN-α which act in antiinfectious mechanisms, while Th2 produce cytokines (IL-4, IL-5, IL-6, IL-9 and IL-13) that mediate allergic response (Gauvreau, 2011).

Airway obstruction can be determined by a variety of causes, such as bronchial constriction, airflow edema, mucus plugs or bronchial remodeling. Acute bronchoconstriction is due to IgE dependent mediator release secondary to aeroallergens exposure, as primary early asthmatic response. Mucus plugs and airway remodeling are associated with substantial changes, leading in overinflation, which improves maintenance of the air flow, but alters the pulmonary mechanics and the breathing's load (Ferrri, 2016).

This compensatory mechanism is limited and when the tidal volume attains the value of the dead space alveolar hypoventilation occurs. Variable airflow resistances are responsible of uneven air distribution, resulting in ventilation-perfusion mismatch, with reactive vasoconstriction. Initially hypercarbia is prevented by CO_2 diffusion through alveolar capillaries' membranes. When airflow obstruction and ventilation-perfusion mismatch aggravates CO_2 retention occurs, with respiratory alkalosis resulting from hyperventilation and later with metabolic acidosis, as a result of increased respiratory workload, increased cardiac output, decreased alveolar ventilation and CO_2 retention (Morris et al, 2019)

Treatment of asthma includes management of the acute episodes and control of chronic symptoms. Pharmacological treatment consists in control agents, such as long-acting bronchodilators (beta-agonists and anticholinergics), inhaled corticosteroids, theophylline,

leucotriene modifiers and newer therapeutic agents, such as anti-immuneglobuline IgE antibodies and anti-IL-5 antibodies.

Acute episodes are managed with short-acting bronchodilators, Ipratropium and corticosteroids. The intensity of the treatment is based on symptoms' severity.

In current guidelines (GINA, 2019) severe asthma encompasses a subset of difficult to treat asthma which remains uncontrolled, after adjustment for contributing factors and maximization of therapy. Acute exacerbations request inhaled bronchodilators, inhaled and oral corticosteroids. In order to prevent exacerbations, patients' therapy requires inhaled corticosteroids and a short-acting bronchodilator as chronic medication, a short-acting bronchodilator as rescue therapy, along-acting muscarinic drug, a leukotriene antagonist and biologic therapy (Highley et al, 2019).

Severe asthma occurs in 3% to 10% of patients, but it accounts for 60% of total costs attributed to this disease (Hekking et al, 2015; Chung. et al, 2014; Sadatsafavi et al, 2010). Its costs are higher than those of diabetes mellitus or chronic obstructive pulmonary disease (Sadatsafavi et al, 2010; O'Neill et al, 2015)

Asthma severity and asthma control are different notions (Chung et al, 2014). Asthma control refers to the degree symptoms are controlled, while asthma severity supposes an intense disease process (Highley et al, 2019). A patient can have mild asthma and be refractory to treatment and poorly controlled, while another may have severe disease which is controlled and treatment responsive.

One says a patient has uncontrolled asthma (GINA, 2019) when she or he has poor symptom control, with frequent rescue medication use, limited activity by symptoms and nocturnal awakening due to dyspnea or has frequent exacerbations (with 2 or more periods of oral corticoids a year or one or more hospitalizations due to asthma).

Difficult to treat asthma supposes that the patient remains symptomatic, despite compliance, medium or high dose inhaled corticosteroids and a second bronchodilator, he requires oral corticosteroids or remains uncontrolled, despite this (Chung et al, 2014). Severe asthma is a kind of difficult to treat asthma in which the patient's symptoms remain uncontrolled, despite addressing contributing factors and adherence to maximal optimized therapy (Hekking et al, 2015). Severe asthma is still referred to as asthma emergency, status asthmaticus, severe refractory asthma or asthma attack (Highley. et al, 2019).

First assessment of difficult to treat asthma should include the confirmation of the diagnostic of asthma through spirometry, pinpointing reversible bronchial obstruction (Israel et al, 2017; GINA, 2019). When baseline spirometry is normal, one should perform bronchial provocation tests.

Secondly one should assess factors that induce symptoms or determine exacerbations. Modifiable factors, such as smoking, poor inhaler techniques, noncompliance, environmental factors or comorbidities (gastro-esophageal reflux, rhinosinusitis, sleep apneea, cardiovascular disease) must be addressed (Highley. et al, 2019).

Last, interdisciplinary team is needed to optimize therapy (Israel et al, 2017; GINA, 2019). Patient education is important and should include data on asthma disease, correct inhaler technique and home control environment (Highley et al, 2019). Optimization of therapy supposes long acting beta-agonist, high dose inhaled corticosteroid, rescue therapy with a short-acting beta-agonist plus add on long-acting muscarinic agent or a leukotriene

receptor antagonist and referral to an asthma specialist (GINA, 2019). Additional nonfarmacologic interventions suppose mucus clearance, vaccination and weight loss.

When severe symptoms persist despite optimization of therapy a specialist should assess the specific asthma-phenotype (allergic versus eosinophilic). This includes blood and sputum eosinophiles, serum immunoglobuline E, skin-pricking tests and when possible fractional exhaled nitric oxide. Add-on therapy with biologic agents addressing inflammation involving Ig E (such as omalizumab - Marcus, 2006; Busse. et al, 2011; Hanania et al, 2011), interleukine IL-5 (mepolizumab – Ortega et al, 2014; Bel et al, 2014; Pavord et al, 2012; reslizumab – Castro. et al, 2015) and IL-5 Rα (benralizumab – Fitzgerald et al, 2016; Nair. et al, 2017;) and α-receptors of IL-4/IL-13 (dupilumab – Castro et al, 2018; Rabe et al, 2018) can reduce the risk of exacerbations.

Patients not selected for biological therapy can be addressed for bronchial thermoplasty (Castro et al, 2010; Highley. et al, 2019).

When symptom control is achieved, the same therapy should be maintained for 3 to 6 month, trying afterwards to reduce it, stopping oral corticosteroids and add-on therapy, reducing inhaled corticosteroids to moderate or low dose and in the end considering to stop biologic treatment (Highley. et al, 2019).

Omalizumab (humanized murine IgG antibody anti-Fc component of IgE), Mepolizumab (humanized IgG kappa antibody specific for IL-5), Reslizumab (IgG kappa monoclonal antibody inhibiting IL-5), Benralizumab (an IL-5 receptor α-directed cytolitic membrane antibody) and Dupilumab are newer pharmacologic agents that can be used as add-on therapy to corticosteroids for asthma control. They reduce the number of acute exacerbation and improve symptoms. Main limitations include treatment's costs and possible occurrence of allergic side-effects.

Anti-IL-13 antibodies are currently assessed in clinical studies for their potential therapeutic role in uncontrolled asthma. Tralokinumab is a human monoclonal IgG4 anti IL-13 antibody that recently demonstrated maximal efficiency in patients with highest levels of IL-13 in sputum in Phase ll trials.

OVERVIEW OF THE STUDY

The commented trial was a Phase IIa proof-of-concept 24-week study evaluating the efficacy and safety of Tralokinumab in patients with moderate-to-severe uncontrolled asthma over a 12-week dosing period (ClinicalTrials.gov identifier: NCT00873860). Three different doses of Tralokinumab were given subcutaneously every 2 weeks, compared to placebo.Patients were receiving maintenance therapy (inhaled corticosteroids, long-acting β2 agonistsand cistenyl leukotriene antagonists).

Primary end-point was changes in Asthma Control Questionniare (ACC) at week 13 of the study from baseline, and secondary end-points were time to asthma control, time to first asthma exacerbation, use of rescue medication, lung function and health related quality of life (HRQL), sputum IL-13 content and Tralokinumab pharmacokinetics.

3.2.2. **COMMENTS**

Although Tralokinumab was associated with ACC improvement compared to placebo, it was not statistically significant. The maximum effect was noted in subjects with high IL-13 sputum. Tralokinumab improved baseline pre-bronchodilator FEV1 compared to placebo, in a dose-dependent manner. Therapeutic effect appeared after first dose and persisted 24 weeks. Compared to placebo Tralokinumab reduced significantly the use of rescue medication at 12 weeks, this effect persisting 12 weeks after discontinuation of the biologic agent. No effect was noted for reduction of exacerbations and HRQL.

3.2.3. **EXPERT MESSAGES**

- Asthma is a complex inflammatory disease of the airways, in which multiple and complex interactions exist between various inflammatory pathways. In asthma IL-13 has a potent pro-inflammatory alone or via cross-talk with IL-4. Its inhibition with various approaches, such as antibodies, receptor antagonists or modified (variant) cytokines reduces inflammation of airways in animal models.
- Short term clinical studies showed similar results, with effect and beneficence on lung function.
- Most studies demonstrated that cytokines directed monoclonal antibodies were more efficient in some population sub-sets. This happened in sub-sets with biomarkers of up-regulated IL-13 pathway (high IL-13 in sputum, high blood eosinophil counts and high sputum periostin level). However, specific IL-13 blockade can be associated with a compensatory IL-4 pathway up-regulation. Evaluating sputum IL-4 dynamic during anti-IL-13 therapy would be necessary.
- These findings offer the perspective for a personalized therapy in asthma. Therefore, in such patients it is worth attempting to characterize the inflammatory cytokine pattern in serum and in sputum in order to find out which pathogenic pathway is the most suitable for therapeutic blockade.
- Such an approach is justified by various reasons: first, cytokines such as IL-4, -5 or -9when up-regulated are capable of producing similar features as IL-13 overexpression, second, that compounds aimed at blocking such cytokines are under development and could be found efficient in certain population sub-sets and third, their high costs might prevent them for being given to any subject with uncontrolled asthma.

3.3. **ADD-ON INHALED TIOTROPIUM IN SVERE ASTHMA**

3.3.1. **HALMARKS**

In uncontrolled and difficult to treat asthma there is suboptimal inflammation inhibition, so add-on of a drug able to enhance bronchodilation or reduce bronchial inflammation seems logic.

Tiotropium bromide is a long acting anticholinergic drug that is widely used in chronic obstructive pulmonary disease (COPD). Some authors (Antoniu et at, 2011; Short PM. et al, 2012) documented its recent potential efficacy in asthma, as well. Tiotropium persistently ameliorated lung function and reduced severe exacerbation risk, even if it didn't exert a notable effect on symptoms and quality of life (Mansfield et al, 2019) .

Its long term effects in asthma are not yet well known.

The discussed studies assess long term efficacy and safety in poorly controlled asthma in patients under inhaled long acting β-2 agonists and inhaled corticosteroids. In such patients add-on medication is required in order to ameliorate symptoms and disease control.

OVERVIEW OF THE STUDIES

We discuss the results of 2 studies (PrimoTinAsthma 1 and PrimoTinAsthma 2), assessing the efficacy and safety in patients with uncontrolled asthma on inhaled long-acting beta2 agonists and inhaled corticosteroids (Kersten et al, 2012).

These two studies, PrimoTinAsthma 1 and PrimoTinAsthma 2, had a similar design. They were both randomized, double-blind, placebo-controlled, parallel group and a study period of 48 weeks. Eligible were subjects aged 18 - 75, diagnosed with an asthma for at least 5 years, an asthma control, questionnaire (ACQ-7) score of at least 1.5 and persistent airflow obstruction (defined as a post-bronchodilator forced volume in 1 s (FEV1) % predicted of 80% or less and a FEV1/FVC ratio of not > 70%) while receiving inhaled corticosteroids at a dosage of at least 800 μg/daily combined with inhaled long acting beta-2 agonists. Eligible subjects were required to have had at least one exacerbation during the previous year and be nonsmokers. Excluded were subjects with COPD, serious comorbidities or concomitant inhaled anticholinergic therapy.

The study medication was represented by two puffs (2 x 2.5 = 5 μg) of inhaled tiotropium delivered via Respimat or matching placebo. Other medications such as anti-IgE, systemic corticosteroids, leukotriene modifiers or methylxantines were allowed.

There were three primary endpoints: peak (maximal) FEV1 response within the first 3 hours after administration and the trough (end of the daily therapeutic effect) FEV1 at week 24 expressed as change from baseline FEV1 and by time to the first severe asthma exacerbation.

Among the secondary endpoints included were the peak and trough FEV1 and FVC at each scheduled visit, AUC for 3 h after administration of the study maintenance therapies for both FEV1 and FVC, time to first asthma worsening and quality of life.

A total of 912 patients were randomized (459 in study 1 and 453 in study 2). Per protocol population included 413 patients in study 1 (202 placebo, 211 Tiotropium) and 401 in study 2 (203 placebo, 198 Tiotropium). In the pooled data analysis the mean age at baseline was 53 years, most of the patients enrolled were female (60.4%), median duration of the disease was 28 years and about 19% of the patients experienced at least three exacerbations during the previous year.

The mean baseline ACQ-7 score was 2.6, whereas the mean post-bronchodilator FEV1%pred was 62.2%.

3.3.2. **COMMENTS**

Tiotropium reduced significantly the airflow obstruction, increasing the peak FEV1 by 86 ± 34 ml ($p = 0.01$) in study 1 and 154 ± 32 ml ($p < 0.001$) in study 2. The overall Tiotropium--placebo groups difference in the trough FEV1 was 88 ± 31 ml ($p = 0.01$) in favour of the treatment group, 111 ± 30 ml ($p < 0.001$). Tiotropium also increased significantly the time to the first severe exacerbation (282 days with Tiotropium versus 226 days with placebo) and this corresponded to a 21% reduction of the risk of developing such an exacerbation (hazard ratio 0.79, 95% confidence interval 0.62 - 1.00, $p = 0.03$).

Tiotropium also improved at 24 weeks other spirometric values such as FEV1 over a 24 h period, PEF, PEF variability and reduced the percentage of patients with at least one severe exacerbation (26.9 vs 32.8% with placebo) as well as the number of severe exacerbations per patient per year (0.53 vs 0.66 with placebo, $p = 0.046$).

Tiotropium reduced significantly the risk of the first exacerbation (time to first exacerbation 315 days vs 181 days with placebo, risk reduction 31%, $p < 0.001$).

The improvements in the quality of life were minimal and not clinically meaningful.

A subgroup analysis found that the maximum therapeutic benefit on lung function was obtained in patients with more impaired lung function, who were males, or former smokers.

There were adverse events reported in 73.5% of the patients in the tiotropium arms and 80.3% of patients on placebo. Drug-related adverse events were reported in 5.7% patients receiving tiotropium and 4.6% with placebo. Dry mouth was detected in 1.8% of patients receiving tiotropium and 0.7% in patients on placebo. Cardiovascular side effects detected were represented by supraventricular tachyarrhythmia, atrial fibrillation, coronary artery occlusion, coronary artery stenosis, and ventricular tachycardia, each of them being reported in 0.4% of the patients included in the tiotropium arm in the first study. Serious adverse events were reported in 8.1% of patients on tiotropium and 8.8% of patients on placebo.

3.3.3. **EXPERT MESSAGES**

- Uncontrolled asthma is uncommon and is usually caused by a suboptimally inhibited airways inflammation and/or insufficient bronchodilation.
- Add-on medications able to improve bronchodilation or to reduce airways inflammation can improve the disease status.
- Inhaled Tiotropium is a long-acting anticholinergic which is currently widely used as a COPD therapy.
- Inhaled Tiotropium, when given for longer periods of time, is able to improve lung function and to reduce the risk of exacerbations and in particular of severe exacerbations.
- Tiotropium might be used in uncontrolled asthma not only for its bronchodilating effects but also for its potential anti-inflammatory effects, which were demonstrated experimentally but need to be also detected in the clinical settings.

2.6. THERAPEUTIC MANAGEMENT IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) is a common, chronic and treatable condition.

It is a chronic respiratory disease, with persistent symptoms due to airflow limitation, as a result of toxic exposure, risk factors including smoking and occupational hazards.

COPD is heterogeneous, with multiple risk factors, phenotypes and comorbidities.

Exacerbations and comorbidities contribute to the severity of the disease.

The severity of COPD is classified according to the ratio between forced expiratory volume in one second to forced vital capacity (FEV1/FVC) less than 0.7and FEV1 value compared to the predicted one as mild, moderate, severe and very sever (GOLD, 2019). The classification is detailed in Table 3.1.

Table 3.1. Severity of COPD

GOLD STAGE/Severity of COPD	**FEV1/FVCF and FEV1 from predicted value**
GOLD I Mild	FEV1/FVC <0.7; and FEV1≥80%of predictive
GOLD II Moderate	FEV1/FVC <0.7; and FEV1<80% and ≥50%
GOLD III Severe	FEV1/FVC <0.7; and FEV1>50% and ≤ 30%
GOLD IV Very severe	FEV1/FVC <0.7; and FEV1 <30 % or FEV1 < 50% of predicted with chronic respiratory failure

The GOLD recommendations assign COPD in 4 groups (A, B, C and D) according to the degree of airflow restriction (Table 3.1), the severity of symptoms evaluated with a questionnaire (CAT) and the number of COPD exacerbations experienced in one year.

COPD NONPHARMACOLOGIC TREATMENT

Smoking cessation and avoidance of exposure to air pollutants is recommended in all stages.

Ensuring oxygen saturation > 90% in pulse oximetry is a desiderate. It can be achieved by supplemental oxygen delivery through a face mask. In patients with arterial partial pressure of oxygen ≤ 55 mmHg or oxygen saturation ≤ 88% in pulse oximetry continuous oxygen therapy is recommended.

In patients with excessive sputum secretions who don't expectorate nasotracheal suction is needed, combined with mechanical percussion of the thorax.

Pulmonary rehabilitation is recommended in patients who remain symptomatic, despite maximal medical therapy.

In obese patients weight reduction is highly recommended

.

COPD PHARMACOLOGICAL TREATMENT

According to the severity of the disease and patient's tolerance a step by step pharmacologic approach is recommended in COPD. In order to assess severity of breathlessness the mMRC Questionnaire (Modified British Medical Research Council questionnaire) is used. The mMRC is figured in Table 3.2.

Table 3.2. The mMRC Questionnaire on breathlessness in COPD

mMRC Grade 0	Breathless only with strenuous exercise
mMRC Grade 1	Breathless on hurry on the level or walking up a slight hill
mMRC Grade 2	Breathless comparing with people of same age walking on the level or having to stop
mMRC Grade 3	Need to stop for breathing after 100 m walk or after some minutes on the level
mMRC Grade 4	Living indoor or breathless when dressing or undressing

Not only spirometry, but also history of moderate or severe exacerbations and their number are also important for assessing COPD's severity. GOLD grades provide information on airflow limitation (spirometry grade 1 to 4), while letters (A to D) offer data on symptom burden and risk of exacerbations and are used to guide therapy.

Patients in group A need an inhaled short-acting β2 agonist or a short-acting anticholinergic for intermittent, mild symptoms, while those in group B need to have chronic long-acting β2 bronchodilators or a long-acting anticholinergic agent.

Patients in group C and D are recommended pulmonary rehabilitation. They are at high risk for developing exacerbations and must receive a long-acting anticholinergic drug or a combination of inhaled corticosteroid and long acting β2 sympathomimetic agent.

Bronchodilator medication alleviates symptoms, increase quality of life, ameliorate exercise capacity and decrease the risk of exacerbations. Inhaled β2-symathomimetics and anticholinergics can be used in COPD patients in stable state and FEV1 between 80% and 60% of predicted value. This medication is recommended for those symptomatic patients with FEV1 less than 60% of predicted value. These drugs must be used as monotherapy, depending on patients' preference, economic considerations and adverse effects.

Short-acting β2-sympathomimetics (Albuterol MDI) and short-acting anticholinergics (Ipratropium) can be used in mild form of disease, with variable manifestations. They are also available in combination in one inhaler (Combivent).

Long-acting inhaled bronchodilators are recommended in cases with continuous mild to moderate respiratory symptoms. Tiotropium, a long-acting anticholinergic used once daily is superior to the long-acting β2-agonist (LABA) Salmeterol in cases of moderate to severe COPD. Other LABAs are Olodaterol, Aclidinium and Indacaterol; they are used to treat peristenty bronchospasm associated with moderate to severe forms of COPD. Aclidinium is safe in patients with associated chronic renal disease, while Indacaterol and Oladaterol are convenient due to their once daily administration. These drugs can prolong QT interval on EKG, with arrythmogenic risk and need caution when associated with β-blockers.

Inhaled corticosteroids (Fluticasone, Budesonide, Triamcinolon) are added in moderate to severe disease forms in order to reduce exacerbations. They are recommended in patients with 2 or more annual exacerbations or in those who have FEV1 less than 50% of predicted value. Their efficiency in COPD is still controversial. There are studies that conclude that inhaled steroids induce a modest symptom reduction and decrease exacerbations, while others pinpoint that steroids don't have any effect in COPD, but are reserved for patients with moderate and severe airflow limitation and constant symptoms, despite maximal inhaled bronchodilator treatment. Inhaled steroids are associated with increased risk of pneumonia and have no influence on 1 year mortality in COPD.

Roflumilast is a phosphodiesteraze inhibitor with anti-inflammatory properties that reduces the risk of exacerbations, but has no bronchodilator effect, so it is not recommended in acute bronchospasm episodes.

Scientific respiratory European and American societies (ACP- American College of Physicians, ACCP – American College of Chest Physicians, ATC – American Thorax Society and ERS – European Respiratory Society) recommend that inhaled bronchodilator therapy should be started in symptomatic COPD patients with FEV1 less than 60% of predicted value. These patients need chronic oxygen supplementation and rehabilitation therapy when they associate rest hypoxemia (PaO2 less than 55 mm hg and SpO2 less than 88%).

During exacerbations COPD patients must receive aerosolized β2-agonists (Albuterol) or anticholinergic solution (Ipratropium bromide), associated with a short course of systemic corticosteroid: oral Prednisone 40 mg/day, for 5-14 days. Longer courses don't increase benefit and may produce harmful side-effects.

Bacterial infection exacerbations are treated with antibiotics, such as Azithromicine, Levofloxacine, Amoxicilline-clavulanate, Trimethoprim-sulfametoxazole, Doxycycline or Cefuroxime. Antibacterial drugs are needed when sputum is purulent and PCR level is over 30 mg/l.

Mucolytic drugs are generally ineffective. Optimal hydration is needed to increase sputum fluidity and promote expectoration.

In patients with hypoxemia noninvasive positive pressure ventilation reduces the risk or the need for endotracheal intubation. It can't be used in patients with hemodynamic instability and reduced consciousness level, severe respiratory acidosis, uncooperative patients. Nasal mask is better tolerated. Oxygen must be delivered at a debit of 10-15 l/min. Monitoring is done with vital signs and arterial blood gases and pulse oximetry.

Aminophylline is controversial, due to its risky side effects and when given needs close assessment of blood concentration (recommended 8-12 mcg/ml) to prevent tachyarrhythmia's appearance.

In patients with secondary erythrocytosis phlebotomy to Ht less than 52% and oxygen replacement therapy are indicated.

Lung volume reduction surgery or single lung transplant can be considered in end-stage emphysema phenotype, with FEV1<25% of predicted value after bronchodilator inhalation complicated with respiratory insufficiency and severe pulmonary secondary arterial hypertension.

Five-year survival is less than 25% after the first episode of respiratory failure. Development of cor pulmonale, pulmonary arterial hypertension, hypercapnia and persistent tachycardia are poor prognostic factors.

In all COPD patients yearly influenza and anti-pneumococcal vaccines are recommended.

Early antibiotic administration improves clinical evolution in COPD exacerbations.

BODE index allows a better assessment of COPD severity, morbidity and mortality, taking into account not only FEV1 reduction, but also systemic manifestations of the disease, quantified by MMRC score (see Table 3.2).

3.4.1. **HALLMARKS - ANTICHOLINERGICS AS ADD-ON THERAPY IN SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

COPD requires for therapeutic control in stable state bronchodilators such as inhaled long-acting beta-2 agonists or anticholinergics and inhaled corticosteroids. These drugs are available as monotherapies or as combination tehrapies in one inhaler, with the advantage of a better patients' adherence to treatment. This pharmacological approach controls symptoms and ameliorates the quality of life (Singh D et al, 2019). A triple extrafine formulation inhaler combination of corticosteroids (beclometasone dipropionate = DBP)/long-acting beta-2 agonist (formoterol fumarate = FF) and long-acting muscarinic agonist (glycopyrronium = G) was assessed in three large 1 year studies regarding efficacy and safety in COPD compared with double inhaled therapies.

In TRILOGY trial (Singh D et al, 2016) the triple inhaled combination conferred superior bronchodilation compared with double BDP/FF therapy, almost a quarter (23%) reduction of COPD's exacerbations and significant improvement in general health status as evaluated with St George's Respiratory Questionnaire.

In TRINITY trial (Vestbo J et al, 2017) the triple combination proved superior to inhaled tiotropium, a 20% reduction of exacerbations and superior health status.

In the third study, the TRIBUTE trial (Papi A et al, 2018), the same triple association of drugs reduced exacerbations with 15% compared with the double therapy indacaterol/glycopyrronium.

However, COPD is an evolutive disease and this is why it is important to know whether a drug is able to delay the clinical deterioration on short and long-term evolution of the disease. As a result, the concept of "clinically important deterioration" (CID) was developed (Singh D et al, 2019). It encompasses a number of clinical variables which can assess short-term and sustained worsening.

CID was used to compare the efficacy of different dual inhaled therapies, such as combination of long-acting beta-2 agonists and long-acting muscarinic agonists versus long-acting beta-2 agonists and inhaled corticosteroids or monotherapies with either long-acting bronchodilators (Singh D et al, 2016; Anzueto A et al, 2017; Maleki-Mazdi MR et al, 2017; Singh D et al, 2017; Anzueto AR et al, 2018; Greulich t et al, 2018). CID was used to compare long-acting muscarinic agonists with placebo (Rabe KF et al, 2017) or triple therapy

with double inhaled combination corticosteroids/long-acting beta-2 agonists (Naya I et al, 2017).

The use of CID as endpoint is that it assesses the clinical deterioration at individual level (Singh D et al, 2019). Its appearance in the first 6 to 12 months of an interval of 3 years follow up period is associated with an increased risk of exacerbations and mortality and predicts a loss in FEV_1 and general health status (Naya IP et al, 2018; Singh D et al, 2019).

Our study evaluates the results of FULFIL trial (Lipson DA et al, 2017), which compared triple fixed inhale therapy (long-acting beta-2 and muscarinic agonists and inhaled corticosteroids in one device) with double therapy (inhaled corticosteroids and long-acting beta-2 agonist in one device).Therapy with inhaled long-acting beta-2 and muscarinic agonists and corticosteroids are prescribed in COPD used alone or in a combined regimen based on various prescribing indications such as the existence of frequent exacerbations, the severity of the airways obstruction, and the existence of a certain disease phenotype. A maximal therapeutic effect with inhaled therapy is thought to be obtained when triple therapy is applied. However, until recently this could only be achieved using two inhalers, and this approach is not always easy to follow by the patient. Therefore triple therapy in one inhaler has been investigated in various forms and trials.

OVERVIEW OF THE STUDY

The FULFIL trial was a phase III randomized double-double-blind, multicentric study which compared the effects of once-daily triple therapy including fluticasone furoate/umeclidinium/vilanterol 100 μg/62.5 μg/25 μg (FF/UME/VI in Elipta Inhaler©) with inhaled corticosteroid (ICS) and long-acting-β2-agonist (LABA) combination represented by budesonide/formoterol 400 μg/12 μg (ICS/LABA: BUD/FOR in Turbuhaler©) which was dosed twice daily (Lipson A et al, 2017)..

The intention to treat population included 1810 COPD patients, 911 in the FF/UME/VI arm, and 899 in BUD/FOR arm which received the study treatments for 24 weeks. A subset of 430 patients, 210 in triple therapy, and 220 in combination therapy remained with blinded therapy up to week 52 (and was labeled as extension (EXT) population). Inclusion criteria were mainly represented by age at least 40, class D GOLD (FEV1 less than 50% and with CAT score at least 10 or FEV1 more than 50% but less than 80%, CAT score of at least 10 and either at least 2 moderate exacerbations over the last 12 months or at least 1 severe exacerbation during the same period). Patients were excluded if they had asthma overlap syndrome, respiratory tract infection, or severe COPD exacerbation.

The two primary endpoints were represented by the changes from baseline in trough FEV1 and by the changes from baseline in health status (which was assessed with the Saint George's Respiratory Questionnaire). Secondary endpoints were mainly represented by the proportion of patients with changes from baseline in trough FEV1 or in health status, which were clinically meaningful (i.e. amounted at least 100 ml for the lung function or at least 4 units of score decrease for health status). Other secondary endpoints were represented by the changes from baseline in respiratory symptoms (measured with Evaluating Respiratory Symptoms in COPD score, E-RS) and by the proportion of responders (i.e. patients exhibiting clinically significant response in lung function respectively in health status). Safety endpoints

were also included. Efficacy and safety were evaluated at week 24 in the ITT population and at week 52 in EXT population.

3.4.2. COMMENTS

This study reports the superior efficacy on lung function and health status of triple combination encompassing a long-acting anticholinergic, a beta2-agonist and an inhaled corticosteroid when compared to combination therapy of the latter two classes in patients with advanced COPD or in patients who were frequent exacerbators.

The study although not having the most appropriate duration for measuring the dynamics of the exacerbations rate used an appropriate surrogate measure, the annualized rate of moderate to severe COPD exacerbations, that is, those who are the most significant component of the morbidity burden in this disease.

Both triple therapy and combination therapy were well tolerated and associated with low incidence of adverse events. There was an extension phase of the study up to 52 weeks which involved a smaller sample (EXT population) randomly selected and with baseline characteristics rather similar to those of the ITT population.

Similar efficacy and safety results were found in the EXT sample.

However, the study also enrolled patients with no or with 1 exacerbation during the last 12 months corresponding to class B COPD. The endpoints discussed above were not analyzed according to this classification to better delineate the efficacy of triple therapy strictly in class D COPD patients (Suissa et al., 2017; Fabbri et al., 2017).

Such an analysis would have been helpful to demonstrate the potential advantages of a triple inhaled therapy approach in frequent exacerbators with more preserved lung function.

The superior efficacy of the triple therapy (with two inhalers, or open triple) was demonstrated previously but against long-acting anticholinergic component alone: in a 12-week study in which 660 patients were enrolled, budesonide + formoterol added to tiotropium were superior to tiotropium alone in improving lung function, health status, and in reducing exacerbations rate (Welte et al., 2009).

Subsequently a 52-week study compared the efficacy and safety of (beclomethasone + glycopyrronium + formoterol) versus beclomethasone + formoterol.

The triple therapy reduced the incidence of moderate-to-severe COPD exacerbations and improved airflow limitations compared to the double therapy which was demonstrated to produce more modest effects (Singh et al., 2016).

More recently another fixed triple combination (beclomethasone + glycopyrronium + formoterol) was compared with beclomethasone + formoterol added to tiotropium (open triple) and to tiotropium alone in a 52-week study and it was found that both triple therapies were superior to tiotropium alone in reducing exacerbations rate and in improving lung function (Vestbo et al., 2017).

3.4.3. **EXPERT MESSAGES**

- COPD is a disease in which currently many efforts are made to identify new therapies which should be able to produce a potent and sustained bronchodilation on the one hand and which should significantly reduce the chronic airways inflammation. The existing therapies are not able to reduce this to an extent which should be reflected by a reduced decline in lung function and hence are not able to interfere significantly with disease aggravation.
- Furthermore some COPD patients have a propensity for more frequent exacerbations despite optimal therapy. Such patients have more severe respiratory symptoms, poor quality of life, and clinically meaningful extrarespiratory symptoms, such as fatigue during stable phase (Antoniu et al., 2015; Antoniu et al., 2016)].
- The conventional therapy for stable COPD is mainly based on inhaled therapy irrespective of the severity of airways obstruction, the step-up approach actually being used when the existing therapeutic regimen is associated with frequent exacerbations or with disturbing residual respiratory symptoms. This means that if a patient who was started on a long-acting bronchodilator has a suboptimal control of the disease, then another long-acting bronchodilator from a different class should be added.
- Bronchodilator combinations in one inhaler offer the major advantage of a more facile dosing, a user friendliness of one device as compared to two and consequently a better adherence to therapy. When the bronchodilator combination is not able fully effective and when the number of exacerbations increases, then the addition of an inhaled corticosteroid is necessary.
- This is currently done most commonly by using one inhaler with long-acting beta-2 agonists and inhaled corticosteroid associated to one inhaler containing a long-acting anticholinergic. Only very recently the triple therapy in one inhaler became available in the EU and this means that patients requiring a triple therapy still have to use two inhalers. Most of the investigational triple combinations including the one featured in this analysis are to be used once daily a fact that is again an advantage if the patient has other comorbid conditions and a complex daily therapeutic regimen.
- One of them, which is in fact freshly authorized within the European Union (beclomethasone/formoterol/glycopyrronium), is to be dosed twice daily, and this makes it very useful for patients with symptoms which increase in severity during night or early in the morning.
- The results of the FULFIL trial demonstrate the efficacy of triple combination and enlarge the existing body of evidence demonstrating the need for earlier triple therapy in patients with preserved lung function but who are frequent exacerbators.
- However, this should be further assessed in subsequent studies enrolling such patients (i.e. with FEV1 predicted 50–80%) and following them up for longer periods.

3.5.1. **HALLMARKS - ANTIINFLAMMATORY THERAPY AS AN ADD-ON TREATMENT IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

One of the main objectives in patients with COPD is to reduce the frequency of exacerbations.

The current guidelines recommend inhaled bronchodilators and corticosteroids as main therapy in COPD, alone or in combination, depending on the stage of the disease (GOLD, 2019).

Roflumilast is an anti-inflammatory drug used as add-on therapy in advanced COPD with chronic bronchitis phenotype, in order to reduce exacerbations.

Large clinical trials can help identify the predictors of its efficacy in different categories of patients with COPD.

Our article was a post hoc pooled analysis of two large randomized controlled studies – the RESPOND (Martinez FJ. et al, 2018) and REACT (Martinez FJ. et al, 2015) trials.

OVERVIEW OF THE STUDIES

The REACT trial was a 54 weeks multicenter phase III-IV placebo-controlled study which assessed the efficacy and safety of roflumilast 500 μg added to a fixed dose of a combination of inhaled long-acting beta$_2$-agonist and corticosteroid and if needed a long-acting muscarinic agonist in severe COPD patients that had at least 2 exacerbations in the last year. The RESPOND trial was a phase IV study with a similar design.

The primary end point was represented by the number of moderate or severe COPD exacerbations per patient and year, Secondary end-points included the rate of severe exacerbations, the number of exacerbations requiring antibiotics and changes from the start FEV1.

The pooled intention to treat population in the two studies included 4287 patients (2147 on roflumilast and 2140 on placebo); 64% patients had severe COPD and 56.9% received long-acting muscarinic agonist. A percentile of 32% had at least one hospital admittances in the last year and 19.5% had a starting eosinophil count ≥ 300 cells/μl.

Pre-specified criteria to evaluate efficacy of roflumilast included:

- Blood eosinophil count (≥150 cells/μl versus<150 cells/μl or <150 cells/μl versus 150-<300 cells/μl versus ≥ 300 cells/μl)
- Number of exacerbations a year (2 versus>2) and
- Number of in hospital admissions for COPD exacerbations (0 versus1).

3.5.2. **COMMENTS**

- Roflumilast was associated with a significant reduction in exacerbations per patient per year. The most important therapeutic effect was obtained in patients with at least one hospital admittance in one year and an eosinophil count ≥ 150 cells/μl.
- The severe exacerbation rate was significantly reduced in patients with COPD exacerbations that required hospitalization, in patients with more than 2 exacerbations and in those with ≥150 eosinophiles/μl.

- Concerning safety, the most frequent (20%) adverse events with roflumilast included diarrhea, nausea, pneumonia, headache and weight loss. Adverse effects in placebo arm were also 20%. Mortality rates were also comparable: 2.1% in roflumilast and 2% for placebo.
- It is needed to characterize better the subpopulations of COPD in which roflumilast add on therapy may carry the most important efficacy. In practice, such populations can be defined according to phenotype (chronic bronchitis and frequent exacerbations) and endotype traits (increased eosinophilia). Older studies have shown that inhaled combination of long-acting beta 2 agonists and corticosteroids were able to reduce mortality and improve COPD status in patients with less impaired airway obstruction – GOLG II stage (Jenkins CR. Et al, 2009). Adding roflumilast could further reduce morbidity, reducing the rate of exacerbations in COPD.
- Because better effect of roflumilast was associated with increased eosinophilia suggests that eosinophil' count can be used as a marker of efficacy. Another point is that roflumilast could be used in asthma-COPD overlap syndrome (ACOS).
- There are publications that report improvement of lung function in asthma patients when roflumilast was added to inhaled corticosteroids (Meltzer EO et al, 2015). A 15 week study (ROBERT) adding roflumilast in patients with COPD stage II and III reduced eosinophil count in the airways (Rabe KF. et al, 2018).

3.6. BIOLOGIC THERAPY WITH NIVOLUMAB IN LUNG CANCER

3.6.1. HALLMARKS – PARTICULARITIES OF NON-SMALLCELL LUNG CANCERS AND BIOLOGIC THERAPY

Mortality due to oncologic conditions continues to ascertain lung cancer as the main cause in men and just after breast cancer, in women. Worldwide the epidemiology continue to be alarming as total numbers persist to be bad due to shifts between developed and emerging economies, developing countries and also due to the contribution of increased lung cancer incidence rates in female patients (Barta, et al., 2019).

According to Eurostat 2015 Source (hlth_cd_aro and hlth_cd_asdr2) death in European Union population has lung cancer as way of representation in 5.2 % of its total appearance (7.2% among men, 3.4% for women). Among those more than a quarter of a million deaths from cancers, more than one fifth died from lung cancer. (Statistics Explained https://ec.europa.eu/eurostat/statisticsexplained/).

After its diagnosis, the patient survival hope is short, with a 5 year survival rate of only 18% (Siegel et al., 2016).

This outcome, globally associated with lung cancers, can be adjusted by taking into account the histological particularities that associate a specific natural evolution but also associate different responses to the existing treatment, with a more or a diminished response to it. 20% of lung cancers have anatomo-pathological aspect of small cells (SCLCs) and poor survival rates – 5 year survival rate of 6% all surveillance, epidemiology, and end results

stages combined. (Noone et al., 2018). The remaining, approximately 80%, could mean better survival rates - 5 year survival rate of 23% all surveillance, epidemiology, and end results stages combined and are referred as non-small cell lung cancers (NSCLCs). Many anatomo-pathological types of neoplastic cells can be involved, but three histological subtypes dominate the epidemiology: adenocarcinoma (50%), squamous cell carcinoma (40%) and large cell carcinoma (Herbst et al., 2008).

Effective treatment is limited. As lung cancer is strongly associated with tobacco consume (https://www.wcrf.org/dietandcancer/cancer-trends/lung-cancer-statistics) a reasonable ante-factum intervention is represented by a status of nonsmoker or successful smoking cessation programs. Post-factum, once lung cancer is already present, an early diagnosis could help effective interventions. But, in the great majority of cases diagnosis occurs in advanced form of disease (Zappa et al., 2016; Zugazagoitia et al., 2017).

Once a neoplastic condition appears in an organism, the affected structures should be promptly removed from the body and such situations appear not as infrequent as we might think. When organism fails in this surveillance, surgical resources can be of used instead. Surgery must satisfy removal of all affected cells while enough tissues remain in place to assure a functional, living organism because with this procedure normal cells are removed along with the impaired ones. In advanced stages, removal of neoplastic structures through bistoury involves unacceptable loss of tissues, seldom effective and feasible. Due to these aspects, a more selective removal solution targeting only the affected structures is highly demanded. Targeted therapies on actionable mutations are now available as NSCLCs express such mutations, EGFR mutation, ALK rearrangement, ROS1 rearrangement or BRAF mutation (Silva et al., 2017).

Nivolumab is a monoclonal antibody (a fully human immunoglobulin) which blocks the programmed death-1 receptor (G4 PD-1 immune checkpoint). This receptor is expressed on the activated T cells, generating, when stimulated, an inhibitory effect on these cells. By blocking this receptor, the release and the activation of T-cell can be recovered, regaining an essential protective mechanism of the organism, against neoplastic evolution. (Guo et al., 2017). By associating such a potential to reinstall T-cell activity, the use of Nivolumab has expanded to many cancers: non-small-cell lung cancer (NSCLC), melanoma, renal cell carcinoma (RCC), classical Hodgkin lymphoma, squamous cell cancer of the head and neck, urothelial carcinoma and other cancers. (https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf).

Its use is however limited by side effects that vary from general, nonspecific (tiredness; skin rash; musculo-skeletal pain) to life-threatening ones: pulmonary, hepato-intestinal, endocrine (especially thyroidal, pituitary, adrenal glands, pancreatic); renal, skin lesions, brain (encephalitis). (https://www.opdivo.com/advanced-nsclc/about-opdivo/clinical-trial-results).

As a result, scientific answers regarding many aspect of Nivolumab use, not limited to its benefits in oncologic pathologies or those regarding its side effect, are subject of actual and future researches, directions structured in documents belonging to European Medicines Agency or U.S. Food and Drug Administration (https://www.ema.europa.eu/en/documents/rmp-summary/opdivo-epar-risk-management-plan-

summary_en.pdf;
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125554Orig1s000RiskR.pdf).

Lung cancer is the solid tumor associated with the highest clinical and economic burden (Alberg et al., 2013). The existing therapies including pharmacological antitumor agents, radiotherapy and surgery applied according to the oncological stage, histopathological variant and therapy availability have increased the survival rate over the last decades. However, in a significant percentage of cases lung tumors still progress despite aggressive management and rapidly lead to death. In such cases newer therapies targeting relevant pathogenic pathways are needed in order to achieve a therapeutic response.

One such pathway might be represented by the programmed death pathway 1 which currently is under investigation in oncology for the therapeutic value of inhibiting its receptors or its ligands (Brahmer et al., 2015). Nivolumab (ONO- 4538, MDX-1106, BMS-936558) is a fully humanized monoclonal antibody of IgG4 type directed against PD-1 receptor. Unlike conventional cytotoxic therapies which inhibit directly the tumor cells, nivolumab blocks the tumor related mechanisms of immune tolerance represented by the immune checkpoints (Postow et al., 2015). With this blockade the T regulator cells which exert antitumor activities are derepressed and innate tumoricidal mechanisms are activated (Pardoll, 2012; Gettinger et al., 2015). Nivolumab is currently approved in the USA and Japan for the treatment of advanced melanoma and of advanced lung cancer and is evaluated in clinical trials for various other indications including the non-small cell lung cancer (NSCLC) (Brahmer et al., 2012; Gettinger et al., 2015; FDA, 2015). At the time of publication of this paper nivolumab had also received marketing authorization in the EU (Nivolumab BMS®) for the therapy of advanced lung cancer (Agency EM, 2015).

OVERVIEW OF THE STUDY

This study discussed was an open-label randomized phase III trial evaluating the efficacy and the safety of intravenous nivolumab 3 mg/kg every 2 weeks versus intravenous docetaxel 75 mg/m2 of surface area every 3 weeks in patients with advanced NSCLC (Brahmer J et al, 2015). Each therapy was given until the first signs of disease progression or signs of major toxicity (requiring drug discontinuation) were documented. The study included patients with advanced (IIIB or IV) NSCLC (squamous cells) with a prior disease recurrence after a platinum containing chemotherapy regimen and with an Eastern Cooperative Oncology Group score of 0 or 1.

The primary endpoint was represented by the overall survival, whereas the secondary endpoints included the rate of investigator-assessed confirmed objective response (based on RECIST criteria), progression-free survival, patient-reported outcomes (lung cancer related symptoms, health status), efficacy and safety. An analysis of PD-L1 biomarker of lung cancer biopsy specimens of the enrolled patients was also performed in order to clearly identify the subset with the best efficacy for nivolumab.

There were 272 patients enrolled, mean age 63, all current or former smokers, most of them (206) men, 135 in the nivolumab treatment arm and 137 in the docetaxel treatment arm. Most of them (217) were stage IV NSCLC patients (105 for nivolumab, 112 for docetaxel). There were 91 patients (48 patients in the nivolumab arm and 43 patients in the docetaxel

arm) with complete or partial response to the previous regimen, 80 patients (33 patients in nivolumab arm and 47 patients in docetaxel arm) with stable disease, 85 patients (44 patients in the nivolumab arm and 41 patients in the docetaxel arm) with progressive disease, whereas in 16 patients (10 patients in the nivolumab and 6 patients in the docetaxel arm) the previous therapeutic response status was unknown. The minimum follow up duration was 11 months and about 34% of the patients previously received paclitaxel. Nivolumab therapy was associated with a better median survival (9.2 months versus 6 months with docetaxel), with a hazard ratio of 0.59 (95% CI 0.44–0.79, $p < 0.001$). The response rate was higher with nivolumab (20 vs. 9% with docetaxel, $p = 0.008$), with comparable time intervals to achieve it (2.2 vs. 2.1 months). The median progression-free survival was 3.5 months for nivolumab versus 2.8 months for docetaxel (hazard ratio 0.62, 95% CI 2.1– 3.5 months, $p < 0.001$). The progression-free survival rate was 21 versus 6%. Complete response was achieved in one patient in the nivolumab group and in no patient in the docetaxel arm, partial response was achieved in 26 patients in the nivolumab arm and 12 cases in the docetaxel group. Stable disease was detected in 39, respectively 47 patients, whereas progressive disease was identified in 56 versus 48 patients. In the nivolumab arm 28 patients received the study medication after initial progression was confirmed with RECIST criteria, and nine of them met the criteria on non-conventional therapeutic benefit (defined as regression from baseline or stabilization of the target lesions after an initial increase in number). PD-L1 was not found to significantly impact the response rates in both study arms. The patient reported outcomes were not analyzed in this paper. The incidence of adverse events was 58% in the nivolumab group versus 86% in the docetaxel group. The adverse events most commonly reported in the nivolumab group were fatigue, anorexia and asthenia (16, 11 and 10%, respectively). In docetaxel treated patients adverse effects included neutropenia, fatigue, alopecia and nausea (33, 33, 22 and 23%, respectively). The incidence of the serious adverse events was 7% for nivolumab and 24% for docetaxel.

3.6.2. **COMMENTS**

Nivolumab was able to significantly prolong survival in patients with advanced NSCLC and to delay disease progression as compared with docetaxel. This paper does not provide information on the antibody's efficacy, lung cancer symptoms and health-related quality of life. These data would have been very useful, especially in the advanced stages of lung cancer. The results are backed up by those of a phase II single arm study, performed in 117 patients to evaluate the effects of a similar dose of nivolumab in patients with refractory NSCLC: in this study clinical response was detected in 17 patients and disease stabilization (with a median duration of the effect about 6 months) in 30 patients (Rizvi NA et al, 2015). Grade 3–4 toxic effects including fatigue, diarrhea and pneumonitis were reported in 20 patients (Rizvi NA et al, 2015). A phase III study (CheckMate-057) comparing the efficacy of nivolumab with that of docetaxel in non-scuamous NSCLC found that the antibody therapy was associated with a significantly higher overall survival, with a better response rate and a PD-1 expression driven response (Paz-Ares L et al, 2015). Unlike the evaluated paper the population in CheckMate-057 was different from a histological point of view and this

might be related to a more clear relationship between the therapeutic benefit and the PD-1 expression.

Nivolumab is a promising immune therapy in NSCLC and this is confirmed by the results of the present study. This antibody, alike ipilimumab, belongs to the so called checkpoint inhibitors, which have proven their potent effects in aggressive cancers, as melanoma or refractory non-Hodgkin lymphoma. Such antibodies have the ability to restore the innate immune surveillance mechanisms against the presence of the tumor through inhibiting the immune checkpoints. In the case of nivolumab, these targets are represented by programmed death 1(PD-1) receptor and ligand, which are both overexpressed and dysfunctional in lung cancer, leading to the inability of the immune system to limit the tumor invasiveness (Sundar R et al, 2014).

The existing clinical data strongly support the use of nivolumab in patients with advanced NSCLC; currently the therapeutic value of this drug is under investigation in further phase III studies, in which this therapy is evaluated as a stand-alone strategy or in combination with the conventional chemotherapy, other checkpoint blockers (ipilimumab) or other antibodies (bevacizumab) (Brahmer J et al, 2015).

This therapeutic positioning can also be helped if the role of PD-1 pathway in the tumor progression is further deciphered. The existing data come from the adenocarcinoma subset of the NSCLC and demonstrate that the up-regulation of this pathway is associated with a more advanced stage of cancer and a poorer overall survival (Zang Y et al, 2014). However, this analysis should be extended to other histological subsets of NSCLC, in order to get a clearer picture of the prognostic value of this biomarker pathway. This should also be prompted by the fact that the above study failed to demonstrate that the upregulation of PD-1 was associated with a better therapeutic response in a subset of squamous NSCLC. Such data would also help to find out if such a therapy like nivolumab would not be better given as an add-on to existing chemotherapy regimen even in earlier NSCLC stages in order to obtain a quicker and more sustained therapeutic response.

3.6.3. **EXPERT MESSAGES**

- Lung cancer is still associated with a high mortality worldwide and the existing therapies are not always able to improve significantly disease outcome.
- Some of the therapies are effective at the first therapeutic attempt and then are no longer able to interfere significantly with disease progression.
- Programmed death pathway was demonstrated to be involved in the pathogenesis of various cancers such as lung, melanoma, especially in the most advanced stages.
- Nivolumab is a monoclonal antibody against the PD-1 receptor which is approved in the USA for the therapy of metastasized or unresectable melanoma and for that of advanced non-squamous lung cancer.
- In phase III studies in lung cancer nivolumab given as a single therapy was demonstrated to improve disease survival and progression free survival compared with platinum-based conventional therapies.Further clinical studies would help to better position this therapy within the existing therapeutic approach.

SECTION II – FUTURE PROJECTS IN THE ACADEMIC, PROFESSIONAL AND RESEARCH FIELDS

1. IMPROVMENTS IN THE ACADEMIC FIELD

I have achieved so far a considerable experience as an academic teacher, both in nursing and internal medicine, along with the clinical experience acquired in internal medicine, at the bed side.

One constant preoccupation during my whole career was to constantly improve my academic and teaching skills. Teaching both nurse students and resident physicians offers me the unique position to work with both future professionals implied in health care. I understood soon that preparing and making them to work as a team is fundamental for the quality of their professional lives. This is why I teach my resident family physicians about the nursing process and nursing profession, so as they can appreciate, work with and respect nurses while treating the patients. I also teach nurse students about medical pathology and therapy, because medical knowledge is essential in their future profession. I always emphasize that nursing diagnostics are not medical diagnostics, but together they represent a valid dual model of caring for the patient, as a team work.

In the future I want to concentrate more on post-registration teaching, in the field of internal medicine for family physicians residents, in editing books with clinical case presentations and electrocardiography assessment of the patients in primary care.

Together with my colleagues I intend to constantly update the teaching material delivered during lectures for nurse students and encourage them to read extra references. I emphasize that they must improve their English language knowledge, because this will allow them to access not only new books and articles in professional journals, but will also enable them to take part in conferences and congresses abroad, not only as simple participants, but also as active lecturers, under our supervision.

Together with my team I also consider to update the textbook for nurse students for clinical nursing. I want to encourage students to deliver presentations in students' congress Congresis, organized annually in our university.

I hope to be able to continue to organize every second year the International Nursing Week, in which speakers from partner universities from Europe and from our faculty will be invited to deliver conferences in English language for our nurse students.

I intend to sustain a mentorship programme for our students and residents, in order to encourage and sustain them in their professional and personal development during their academic education.

Regarding my relationship with the younger members in our discipline I constantly encourage them and stimulate their professional development, as they will be those who will continue to teach and train our future students. I constantly ask them to take on more responsibilities, as they will accede to future higher teaching positions, as Lecturer or Associate Professor.

2. FUTURE PROFESSIONAL DEVELOPMENT

Even if my academic development has always played a major role, my focus also concentrated towards improving my skills and competencies as a consultant physician at the bed side. The importance of feedback from patients regarding the quality of the care received is fundamental for my development as a professional.

I always strived to attend national and international conferences and congresses to keep me informed with the latest knowledge in the field of nursing and internal medicine. I want to use these meetings with my peer colleagues from abroad to promote our university and our discipline as a valuable and credible partner for common future academic and research projects.

I encourage my younger colleagues to attend these scientific sessions and take part not only as passive listeners, but also as active speakers.

I frequently go in Erasmus staff exchange partnerships in other countries (Belgium, UK, The Netherlands, Spain) to contact my peer colleagues, exchange ideas and ways of teaching, especially during the International Nursing Weeks of those partner universities. In these weeks brain storming happens, and it is a source of new ideas for future common projects.

I encourage my colleagues from our discipline to do the same.

I consider that it is fundamental for each member of our teaching staff to see at least once how a hospital abroad functions and how the academic process takes place in the western world.

Another project is to increase our interdisciplinary collaboration with colleagues from our department, because the complexity of the patients we encounter nowadays requests an interdisciplinary team of physicians (internists, geriatricians, nephrologists, infectious diseases specialists, pneumologists, gastro-eneterologists, diabetes mellitus specialists), nurses, dieticians, physiotherapists, social workers and psychologists.

Together we can offer a better approach to patient care and also develop common research projects.

Additionally, I did my best to improve my English language knowledge, passing and promoting the Cambridge exam with C1 (Advanced) qualification, at the age of 54, as a proof of the life-long learning system.

3. RESEARCH PERSPECTIVES

The postdoctoral experience I gained as a researcher will allow me to select and train young and gifted, perseverant students and residents in doctoral studies. Team work is important in scientific research and this is why the development of the students' interest in this field, from a young age is capital.

My personal interest in research will be directed towards nursing, but also internal medicine topics, as follows:

In the field of nursing I will continue to study mentorship, as a tool for fight against academic stress and a possibility to enhance resilience in our students and residents.

In the field of internal medicine I am interested in the way chronic diseases (respiratory and cardio-vascular diseases) impact the patients' quality of life and what can be done to decrease the burden of the disease in everyday life.

3.1. **ACADEMIC STRESS AND RESILIENCE**

Stress is recognized today as one of the most important issues in our lives and a major compound of the modern world. Even if it can have positive effect on people, it can also exert negative effects. In order to preserve a healthy body and mind, people have to face stress correctly. In 1980 Schuler wrote that stress points to important opportunities, limitations or needs faced by individuals and when results are uncertain people develop inside insecurity.

Selye (1983) divided stress in four major categories: over-stress, under-stress, good stress and distress.

- Overstress is encountered when the person's ability to adapt to change is override.
- Under-stress means that the individual's needs are modest and the person lacks a self-achievement desire.
- Good stress supposes that under the stressor's action the individual feels happy and satisfied.
- Distress happens when the stressor makes the individual feel bad and, if chronic, can induce illness.

In the university the teachers favor the acquisition of knowledge by the students and frequently neglect the emotions of learners during the process (Lin YM, 2009). Students may experience unfamiliar and unpleasant feeling, such as nervousness, worry, depression, frustration. These can induce unfamiliar behaviors in students and interfere with the learning progress. It is essential for them to seek support and counseling by teachers, family or friends and peers.

Academic staff itself perceives stress. Evidence favors the opinion that faculty members in medicine are increasingly dissatisfied, unhappy and burned-out (Simpkin, 2019). Academic institutions have a triple role: to provide high quality education for future health professionals, to promote knowledge through research and to offer top clinical care for patients.

An increasing amount of interest has been showed to the impact of stress on academic education of students from different specializations (students of business colleges- Khan, 2013; students in management - Rajasekar , 2013; medical students - Abdulghani, 2008; Radman SA, 2011; Backovici, 2012; Sohail, 2013; Chen, 2013; Bob, 2014; Saravanan, 2014; medical dental students – Saub, 2013; Al-Sowygh, 2013; Al-Samadani, 2013). There is also an important and growing body of references on how stress affects academic achievements in nursing students and how students develop coping strategies against stress (Benavente , 2011; Gurbinder Kaur , 2011; Kumar, 2011; Pulido-Martos , 2011; Sharma, 2011; Oner Altiok , 2013; Labrague, 2013; Khater, 2014; Benavente, 2014; Wolf, 2015).

In 1984 Lazarus and Folkman defined the psycho-social stress as a dysfunctional link between a person and his/her environment, which is perceived as burden exceeding the person's ability to cope and puts a risk on his/hers health. The imbalance between the environment's demands and the individual's resources conduces to stress. The abilities of the person to adapt to stress represent resilience (Card, 2018).

During their theoretical education and afterwards, in their clinical practice, nursing students encounter a variety of stressors (Labrague, 2013). Research showed that nursing students experience a high level of stress (Tully, 2004; Papazisis, 2008; Shriver, 2009). Nursing students have to face a more powerful stress than their peers preparing in medicine, dentistry, physical therapy or pharmacy (Steker, 2004). The most common stressors identified by nursing students relate to their academic training and practice (Evans, 2004; Nolan, 2008), exams and assessments (Gibon, 2007; Pulido, 2012) and the high workload (Chan, 2009).

Once in clinical practice training nursing students face other stressors, such as the new environment, fear of making mistakes in delivering care, lack of professional nursing skills, the need to support the patients physically, but also psychologically and socially, the trauma of seeing a patient die, for the first time. Other stressors can be related to the healthcare team, the fear of being admonished by the staff for lack of practical skills or attitude. As students progress in further year of academic education, the stress also increases and is related to the complexity of care. Sometimes the mentorship relationship is a considerable source of stress for the student. Pryjmachuk (2007) consider that stress in nursing students is a combination of extracuricullar and personal factors and the academic environment.

Stress impacts not only students' academic performance, but can negatively imprint the physio-psycho-social life of the person. It can interfere with the acquisition of new psycho-motor skills (Beddoe, 2004; Hughes, 2005; Labrague, 2013).

Students develop protective and coping behaviors towards stress. When these coping behaviors are effective in diminishing stress they are described as resilience (Card, 2018). Resilience represents the stress coping ability and "the personal qualities that enable one to thrive in the face of adversity" (Connor, 2003).

But there are many other negative behaviors that students can experience, such as: alcoholism and drug dependence, eating disorder, sleep disorders, mental health disorders (Hauton, 2002; Evans, 2004; Labrague, 2013). During their academic education students in health professions can develop burn-out syndrome (Papazisis, 2008; Watson, 2008; Jimenes, 2010; Car, 2018).

In 2009 Lin and Chen imagined, published and validated the Academic Inventory, exploring teachers' stress, results stress, tests stress, studying in groups stress, peer stress,

time management stress and self-inflicted stress. The authors have conceived a 34 items questionnaire in order to explore the students' ability to cope with stress. The affirmations in the test were assessed by agreement or disagreement on a 5 point Likert scale (from total disagreement for 1 and total agreement for 5). The questionnaire collected in the first section general data about the students, such as gender, age, number of siblings, geographic residence, if the subject was right or left-handed, number of children they had, marital status, religion, political beliefs. The second section of the questionnaire included the 34 items reflecting the stressor factors (9 items linked with teacher's stress, 5 items related to examinations' results, 4 items related to tests, 5 items related to group studying, 4 items connected to peers, 3 items related to time management and last 4 items linked with the self-inflicted stress). To be more precise, the stressors explored for each category were as follows:

1. Stress from teachers: including teaching materials, teaching and exercise items.
2. Stress from results: stress from parents, including conflicts between expectations and opinions and drops in grades.
3. Stress from tests: worry about how to prepare for a test and redo the compulsory courses.
4. Studying in group stress: included exercise reports, grouping, etc.
5. Peer stress: included academic competition, peer interferences, etc.
6. Time management stress: social activities and student association, time management and choices, etc.
7. Self-inflicted stress: such as self-expectation, interests of course selection, etc.

The authors concluded that the higher the students' score, the higher the stress score and the lowest the resilience. This questionnaire can detect the factors which promote academic stress and allow the universities to make changes in order to diminish the stressful exposure of their students.

Our study will be conducted in Romanian nursing students in our University and will have as main research directions the following aspects:

- Identify and quantify the level of stress among our faculty's students;
- Identify common and academic stressors;
- Determine the response to stress and degree of resilience among our students.

The results could provide essential and useful data for nurse educators, in order to identify students' problems and facilitate their preclinical and clinical learning and develop efficient interventions and strategies to reduce stress in academic nursing education.

3.2. **BURNOUT SYNDROME IN CLINICAL PRACTICE**

The burnout syndrome is an important condition that affects health care professionals, especially nurses and physicians (Freudenberger, 1974; Maslach, 1996; Simendinger, 1985; Kumar, 2016) who face an exceeding and chronic stress in their workplaces. Freudenberger described for the first time burnout in terms of behavioral and clinical signs. Maslach gave the first definition of burnout in 1996.This condition manifests as emotional exhaustion, depersonalization and low personal achievement (Romani, 2014). It can have a deleterious effect on the individual's professional performance, career development and can negatively

impact care (Shanafelt, 2012). It can also determine patient dissatisfaction and decrease safety, productivity and professional effort.

Physicians and the health system

Burnout is a really important problem, which should be detected before a major incident occurs. It is difficult for physicians to admit they are burnout and need help. Approximately one third of physicians experienced or experience burnout during their career (Shanafelt, 2009). They experience a crisis of professional identity, doubt their efficiency, an excessive workload and insecurity in their job. Physicians are hold responsible for the efficacy of the health system and operational capacity and are held in charge for the patients' outcome. Frequently they have to assist a lot of patients in limited time. The computers and software available seem to create new time-consuming duties for the medical staff, instead of helping them. The regulations and the administrative and bureaucratic requirements make frustrated physicians and nobody cares if these technologies are doctor friendly (Antohe, 2018). Burnout is considered to be an indicator of organizational dysfunction (Maslach, 2018). "An organizational culture embracing core values such as fairness, positive feedback, and avoiding punishment of physicians for speaking out about burnout are cornerstones of moving beyond the problem" says Namita Seth Mohta (Maslach, 2018).

Physicians' autonomy is a beautiful memory nowadays, when insurance companies, hospital administrators and national medical boards decide on how medicine should be practiced. The system is expected to have a maximal productivity. In this context, it's up to physicians to take back their profession and responsibilities. The support of the professional bodies must be more consistent and not profit oriented (Antohe, 2018).

Research on burnout

There is a constant interest and a consistent body of research on this topic over the last decade. Statistics on physicians' burnout in the US have shown a constant increase since 2013, from 40% to 51% in 2017, as revealed by a Medscape survey (Peckham, 2017).

A recent survey published in Mayo Clinic Proceedings reports that burnout and satisfaction with work-life balance had worsened between 2011 and 2014, with more than half of physicians reporting burnout (Shanafelt, 2015).

In the Medscape survey (Peckham, 2017) over 15,000 physicians from 29 medical specialties in USA responded to the questionnaire and offered some surprising results. In this research the highest rates of burnout occurred among physicians from emergency medicine (59%), followed by obstetrics-gynecology (56%) and family physicians, internists, and infectious disease physicians (each with 55%). These specialties deal directly with patients with a range of complex problems. Other studies have also found high burnout rates in these professions (Bell, 2002; Shanafelt, 2012; Ben-Itzhak, 2015). Approximately one in every three physicians is experiencing burnout (Shanafelt, 2009).The gratest rates of burnout were found in surgeons or anesthesiologists (Daniels et al., 2016).

What is more worrisome is that students in medicine and preregistration doctors also experience burnout. In a meta-analysis conducted by Frajerman and presented at the European Psychiatric Association (EPA) 2018 Congress (Abstract OR0050, presented March 5, 2018), involving 16 500 medical students, found out that 46% of subjects experienced burnout, expressed mainly as emotional exhaustion.

A meta-analysis of 5440 English language articles from 2010 to 2017 using Maslach Burnout Inventory as an assessment tool of burnout, 23 studies including 16,769 medical students found out 8011 subjects having an estimated rate of 45.8% of burnout (Maslach, 2018).

The first study on medical residents' burnout was carried 9 years ago. In that meta-analysis that included 19 articles, from 1975 to 2005, the prevalence of burnout ranged from 18% to 82%. The prevalence was higher in countries from Middle-East, probably influenced of poor working conditions, wars and terrorism (Maslach, 2018). Using Maslach Burnout Inventory data showed that 42.2% of students experienced emotional exhaustion, 25.8% - depersonalization and a minority of 21.2% recognized personal accomplishment.

These studies show that there are serious problems and a bad mental health in medical students, before they begin their education as residents. It seems that apparition of burnout is related with the duration of time spent on duties (Maslach, 2018). The pressure put on students to excel and perform is an additional factor favoring the occurrence of burnout. Exam failing constitutes a motif of burnout appearance in medical students (Sibeoni, 2018). Frajerman (2018) and colleagues determined in a meta-analysis that from 8011 medical students in USA and Europe had a prevalence rate of burnout of 45.8%.This prevalence was higher in USA than Europe. Data show that 42.2% of students experienced emotional exhaustion, 25.8% depersonalization and only 21.2% had a sense of personal accomplishment. Burnout is a subject of interest in students and has to be taken in consideration.

Another meta-analysis published in 2016 (Rotenstein, 2016) found that prevalence of depression in medical students was 27.2% and a 11.1% prevalence of suicidal ideation. "So we have no excuse," Frajerman said. "We know there is bad mental health in medical students, even before residency." If there is a will to improve that situation one has to intervene earlier to prevent burnout's appearance because this is the most common symptom and risk factor for depression and dropout in students. It is an individual responsibility of the students to seek help for anxiety and depression, but it is the responsibility of the teaching hospital and medical faculty to intervene to prevent burnout in students.

Physicians' burnout and its sources

When physicians were asked in the Medscape survey in 2017 which are the causes of their burnout syndrome, they invoked too heavy bureaucratic work, spending too many hours at work and the electronic health record as the main causes. They were followed by

insurance issues, fear of malpractice and family stress (Peckham, 2017). Burnout was higher in female physicians (55%).

Physicians' burnout is characterized by a lack of mental energy, labeled as emotional exhaustion. The factors which generate burnout and professional engagement are: workload and job demands, efficiency and resources, flexibility and control over work, work-life integration, alignment of individual and organizational culture values, social support and community at work and the degree of meaning derived from work.

Each of these stressors is influenced by the individual's personality, organization, work unit and national factors. The reduction of the intensity and action of these factors is an individual and organizational responsibility (Peckham,2017). Reducing burnout and promoting engagement is a shared necessity for the individual and the organization. Some health care organizations try to promote changes towards a happier workplace and happier physicians, such as mindfulness training, yoga, psychotherapists, peer groups and mentoring.

Clinical aspects of burnout

The main three symptoms that appear in burnout syndrome include: exhaustion (lack of physical, emotional and spiritual energy), cynicism (loss of empathizing capacity, reduced connectivity with patients, colleagues and staff) and doubt (lack of confidence regarding the importance and quality of your work).

The burnout syndrome evolves in three phases (Shanafelt, 2017).

In the first step the work stress varies daily and symptoms are compensated, having no clinical impact.

In the second phase symptoms get evident. Exhaustion, cynicism and an uncomfortable feeling, in various amounts, appear. Initially symptoms can be inconstant, intermittent, while in a second step the symptoms express more frequently and in a third step they are permanent, while the physician tells himself he is trying to do his best he can and that all colleagues are doing the same.

In the third phase the burnout has a major impact in the doctor's career and also decreases the quality of the physician's personal life. Symptoms are permanent and the doctor contemplates the idea of quitting his/hers profession.

The emotional exhaustion is the major dimension of burnout's clinical aspect.

Physicians in the US experience lower levels of emotional exhaustion compared to their European fellows, due to the safety of professional culture and career development opportunities (Lee, 2013).

Treatment of Physician Burnout

Physicians' burnout syndrome prevention is a never taught desiderate in pre- and post-registration education. Its cure resides in the 3 R action plan (Antohe, 2018), including: to resist, restore and reduce exposure to stress at the workplace. Resist supposes to increase mechanisms of self-defense against the job stress. Restore means to regain the energy lost during work. Reduce exposure implies to diminish the stress in the workplace. There are 4 strategies for that: to decrease the intensity of what the physician is doing, reduce the stressor

not by changing job, but by modifying the way he/she works and, in more severe cases, change job to a position less stressing in medicine or retire or leave job.

In prevention of burnout the professional organization should play a preeminent role. Fighting against burnout necessitates centrally and locally designed interventions (del Carmen, 2019).Solutions should include recognition and accountability from regional institutional leadership, shared commitment from individuals and organizations. Deliberate, sustained and comprehensive efforts by the organization to reduce burnout and promote engagement can make a difference (Shanafelt, 2017).

Victor J. Dzau (2018) and colleagues from the National Academy of Medicine Action Collaborative on Clinician Well-Being and Resilience write in an article published in the New England Journal of Medicine:. "No single organization can address all the issues that will need to be explored and resolved." The authors consider that the National Academy of Medicine is in a favorable position to attract and coordinate the global efforts on clinicians' wellbeing and resilience, already joined by 100 institutions around USA. This network has four central goals: increase the visibility of clinician stress and burnout, improve healthcare organizations' baseline understanding of the challenges to clinician well-being, identify evidenced-based solutions and monitor the effectiveness of the solutions' implementation.

Many health organizations have started to test programs to reduce burnout among the workforce. For example, Standford University School of Medicine has piloted a "time banking" program to compensate physicians for the time spent in activities that fall outside their caregiving duties. In exchange of time spent on task such as mentoring, taking part in different commissions, the Standford's pilot program allowed faculty members to receive work and home related services such as: meal delivery, cleaning services and grant writing support. This initiative was successful especially among female physicians. According to Taint Shanafelt, who joined Standford's Faculty in 2017 as the organization's chief wellbeing officer the program of time banking was an important cultural change.

At Mayo Clinic evaluation of clinicians' wellbeing has become a priority, in order to identify departments and divisions who need support. Physicians are asked to evaluate the leadership skills of their immediate supervisors. Coaching and support services are offered as needed to address performance gaps (Wrights, 2018).

Other organizations have imagined programs which decrease clinicians' non-caregiving tasks. One such example was imagined at the Department of Family Medicine at the Colorado University, a system called APEX (from Ambulatory Process Excellence). Many steps involved in a visit, such as data collection, medication taken, visit documentation, are provided by a medical assistant, letting the providing physician to focus on the patient's exam and medical decision making. With this team based approach within 6 months from APEX implementation burnout rates decreased from 53% to 13% (Wright, 2018).

Interventions to reduce burnout in physicians

Individual interventions against burnout support increased resilience to stress and put emphasis on individual wellbeing. Resilience is the ability to cope with stress, including the abilities that enable one to cope with adversity (Card, 2018). In contrast with burnout the person feels vigorous, dedicated and absorbed in work.

The concept of physician wellbeing is multidimensional, including factors related to each individual, as well as the work environment. Physicians must engage actively in self-care. Physicians' and healthcare organizations should evaluate the balance between the demands placed on physicians and the resources provided to sustain an engaged, productive and satisfied physician workforce (Kuhn, 2017). Global efforts must be implemented to sustain physicians, seeking help for physical and psychological health problems.

Individual efforts should be directed towards family' and friends' support and hobbies as sources of wellbeing and armamentarium against burnout.

Mentorship for medical staff, at pre- and post-registration level could also offer a strong weapon against burn-out.

The research on burnout syndrome will be carried among our students and faculty staff and will assess these main aspects:

- The degree of burnout among students and staff;
- The clinical aspects of burnout;
- The ways subjects use to cope with burnout.

3.3. HEALTH-RELATED QUALITY OF LIFE IN HEART FAILURE PATIENTS

Heart failure, a frequent chronic condition, has a negative impact on health-related quality of life (HRQoL) and this fact is well documented (Juenger, 2002). The improvement of quality of life (QoL) in heart failure is an important objective worldwide, explicit addressed in guidelines (Ponikowski, 2016; Yancy et al., 2013; NIH, 2010).

Symptomatic assessment of heart failure is achieved with NYHA classification, which correlates with the severity of the disease, despite its subjective character (Gallagher et al., 2019). Validated instruments to assess HRQoL in heart failure are used mainly in clinical trials, with little if not none use in clinical daily practice.

HRQoL is determined by a complexity of factors (physical, emotional, social) and in perceived subjectively by each individual (Testa et al., 1996; Gallagher et al., 2019). A structured assessment of HRQoL in heart failure patients is needed in order to develop patient-centered care (Lewis et al., 2001; Gallagher et al., 2019). Patient's perception is the focus of evaluating the specific need for care. The preferences of patients are used to guide care and facilitate shared decision, providing a frame for clinical monitoring (Gallagher et al., 2019).

A reduced HRQoL is associated with poor prognostic, correlating with the need of rehospitalisation and mortality in patients with heart failure (Kosiborod et al., 2007).

There are some instruments developed for assessment of HRQoLin heart failure, generaic and disease-specific. However there is not an agreement on which tool is best and none of them is implemented in daily clinical practice.

The questionnaires in use are: the Minnesota Living with Heart Failure Questionnaire (MLHFQ), EuroQoL 5D-3L and Kansas City Cardiomyopathy Questionnaire (KCCQ).

The MLHFQ includes 21 questions related to heart failure and investigates HRQoL in the previous month. The physical HRQoL consists of 8 questions and the emotional domain of 5 questions. The answers are rated on a 5 Likert scale (0-5), with 5 being the worst adverse symptoms. The higher the score, the poorer the HRQoL.

EuroQoL 5D-3L is a generic health questionnaire. The first part is the health score, which takes in the account the mobility of the patient and her/his capacity to p[erform autonomous the activities of daily living and scores discomfort, anxiety, depression level. The second part is an analogous visual 0-100 scale which as a quantitative self-assessment of the global health of the individual.

KCCQ is a heart failure diseases specific questionnaire which contains 23 questions, including physical and social limitations, symptoms and self-limitations, each rated on a 0-100 scale, a higher score meaning a better status.

In our future research we will seek for correlations between HRQoL and demographic, clinical and biological data from in hospital patients admitted with heart failure, as well as relations with echocardiographic assessment, functional NYHA class and therapy of these patients.

FINAL REMARKS

The opportunity to train and supervise PhD candidates is a strong motivation to continue my oqn development as an academic teacher and as a physician.

Working with young and enthusiastic people I will constantley keep updated with new medical research and discoveries and I will be able to mentor them with interest, curiosity, rigurosit and moral practice.

I plan to further increase our visibility at international level, for both our department and university and promote scientific exchanges.

I want to enhance the visibillity and prestige of Iasi Nursing school, and constantly encourrage my younger colleagues to develop and do so.

SECTION III - REFERENCES

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