HABILITATION THESIS

INTERCONNECTIONS BETWEEN URINARY TRACT INFECTIONS AND STONE INCRUSTATIONS OF THE DOUBLE J STENTS AT THE LITHIASIC PATIENT

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The present work is a synthesis of the main scientific results obtained by the author during 1991 – 2017 in the Department of Surgery, University of Medicine and Pharmacy “Gr. T. Popa” Iasi. It comprises three major parts.

The first part includes some of the results of my research, which I consider to be significant, in the wider context of general knowledge of the particular domain.

The second part addresses the study projects I would like to develop, based on the results I obtained, and also in aim to clarify uncertainties appeared till now in my fields of research.

The third part includes references.

In this context, I would like to thank all my collaborators and mentors for their support and contributions to the results presented in this thesis.

I would like to thank my family for their constant help and understanding during all these years.
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ABSTRACT

My special interest, since I have been a young urologist, is in kidney stones pathology and the result was my PhD thesis presented 22 years ago: ESWL FOR THE TREATMENT OF RENAL AND URETERIC STONES. It was the perfect occasion to present my own invention PC-1 Device, device perfectly adapted to the structure of our KS-88-4 spark gap lithotriptor, used for the radioopaque pelvic stones. This invention, even if is not yet registered as a trade mark, has successfully extended the indications for ESWL for stone in the distal part of the ureter and, more than that, for the Steinstrasse, a complication occurred in treating large kidney stones.

The plans for my future directions of research that I want to develop in the next years are connected with stones, urinary tract infection (UTI) and incrustation of the double J stents. I would like to dedicate my efforts, to a complex study that I hope will bring to light different aspects concerning the most efficient methods to block the process that leads to the incrustation of the double J stents, using different drugs which, in my opinion, may bring benefits.

The ideal double J stent does not exist yet, although many urologic departaments in the world use this device on a daily basis. The attachment of E.coli bacteria to the ureteric stent is a hypothesis little known and discussed but, in my view, it needs a special attention because E.coli has the fimbia, the special component that permits the bacteria to attach itself to the bladder mucosa. The prevention of occurrence of biofilm, the key step towards the incrustation of the stent, is not a process fully understood and despite the progress both in vivo and in vitro, no matter what antimicrobial agent was used, we still do not know much about infection, incrustation and the resistance of the germs that remain a delicate issue. In our study we wanted to observe if the drug Uractiv Litho, used for the prevention of E. Coli adherence to the double J stents is similar to the Cranberry extract which has a demonstrated role in preventing the adherence of the E.coli to the bladder mucosa. We do not want to give our patients antibiotics because the resistance of the biofilm to the antibiotics is well known, but we want to give medication that is known to prevent crystallization in the urine versus medication that prevent the adherence of the bacteria to the bladder mucosa.

The two medications we want to study and compare are already in drug stores and have been used for many years for patients with stones and urinary tract infections (UTI); they have minor side effects and there is no mention about toxic events. First of them is Philanthus niruri and it has a long reputation to dissolve the calculi in the urinary system, so we can presume that this drug can play a role, blocking the development of the matricial mineral zones on the double J stent surface.

The second drug, the cranberry extract, is the only phototherapeutic agent accepted by EAU Guidelines in 2015 and 2016 to prevent UTI. Cranberry has been was used for a long time as a fruit, spice and as a treatment, both as a cranberry juice or as dry extract as tablets. There is a long list of components in cranberries but the main component and the most useful is type A proantocianidin for its effect of antiadhesion of E.coli to the bladder mucosa.

The patients with double J stents will be the beneficiaries of this project because they will have a special occasion to be monitored by a regular programme and the academic community because we will note precisely our observations and, perhaps, we will identify a more efficient strategy to prevent stone incrustation. Another part of the project is focused on the urinary
tract infections (UTI).

I want to start this important programme of research from the reality that Romania occupies the second place in Europe at the use of antibiotics. We will include all the patients with UTI and multi drug resistant (MDR-UTI) in this study. We want to see the connections between previous antibiotic treatments for other infections (ORL, respiratory, etc) and the risk of MDR-UTI, and to start the discussions about the strategies for empiric treatment considering the risk of prescribing empiric drugs that are already resistant for a large category of UTI.

We must have a serious discussion with the other colleagues in the region in order to avoid the recommendation of several very utilized antibiotics nowadays. The goal is to let, for a reasonable period of time, the germs recover the sensibility for the overused antibiotics.

It is clear that this list of banned overused antibiotics should be discussed firstly with all the specialists in the infectious diseases and other doctors who use frequently the antimicrobial drugs and, after a serious debate, the list will represent a guide in our activity.

The patients included in this study will be over 18 years old, with or without double J stents, admitted in the clinic with a confirmation of a UTI.

The main goals of the study will be the identification of the antibiotics that should be, in the specific context of our regional hospitals, temporally abandoned from the daily use as an empiric recommendation in several infections and to design a strategy for the future MDR-UTI challenges. In other words, a plan based on the realities of our daily practice, in order to avoid the MDR-UTI in the future or, at least, to limit their impact.

A secondary goal will be the identification of the factors that can explain the occurrence of these infections that are difficult to treat and the measures needed to be taken to limit the spread into the community.

All my research projects that I intent to make are to be done in "Dr. C. I. Parhon" Clinical Hospital under the supervision of the University of Medicine and Pharmacy "Grigore T. Popa" Iasi with the help of my colleagues from Nephrology and Infection Disease Department. I am convinced that the young specialists and PhD candidates will have many interesting things to research beyond the 2 major projects I have already mentioned, offering the academic community original and useful PhD thesis.
I. LANDMARKS OF THE PROFESSIONAL ACTIVITY

My first steps in urology are connected with two major events at the beginning of 1990: on one hand the beginning of my academic career at the University of Medicine and Pharmacy Iasi and on the other hand the introduction of endourologic procedures and technologies in Romania. Any doctor feels a special attraction for a branch in his field of interest.

One of my special interests was the pathology of kidney stones. I became a young assistant at the Department of Urology in 1991. In that period of time, extracorporeal shock wave lithotripsy (ESWL) and endourologic technologies were freshly introduced in the Romanian University Hospitals and were offering an elegant and successful variant of treatment for the lithiasic patients, far less aggressive than classical surgical treatments. For a young urologist this was a great step forward in learning the new minimal invasive methods from the beginning.

The scholarship as young resident in urology in Amiens, France, in 1991 and 1993 brought me the huge possibility to study with great specialists in the field (Professor Jacques Petit) and to collect a large amount of medical literature, from books to articles, that later became a very important condition for the research in my PhD thesis: ESWL FOR THE TREATMENT OF RENAL AND URETERIC STONES under the coordination of Professor Cicerone Filimon.

The fragmentation of kidney stones has been a turning point in the history of the treatment of kidney stones. The almost impossible dream, at that time, of a group of doctors from Munich (initiated in 1970 by Professor Christian Chaussy in the labs of Dornier) was brought to life on 7 February 1980 when they successfully disintegrated the first 1 cm renal stone.

In 1982, Professor Chaussy and his team published the first article which was as a shock wave for the urologic world: a vast majority of the stones that cannot be eliminated spontaneously will be disintegrated with intelligent shock waves produced outside the body and focused directly onto the stone which was located by X-ray system.

After this first publication another 2 years were necessary for this spectacular procedure to spread across the Atlantic Ocean into USA, and after that in the whole world.

So, in 1992, I have started working with the second generation lithotripter in my department, in an era when the machines were in a continuous development and the possibilities to treat kidney stones were, step by step, larger and the patients coming for this procedure were more and more ready to embrace the new methods of treatment.

My PhD thesis was the place to debate a various number of aspects connected to the ESWL from my own experience, broadened in different centers in Europe (Amiens, Paris, Bruxelles). I have also presented my own invention PC-1 Device, device perfectly adapted to the structure of our KS-88-4 spark gap lithotriptor, used for the radioopaque pelvic stones.

This invention, still unregistered for bureaucratic reasons, made my thesis, the first one in Romania on this subject, to bring a new element, a solution for all the patients that before had no other option than open surgery, an intervention full of possible complications.

The device PC-1 has two interchangeable parts which can put the patient at 90 degrees on the bed of the machine, the X-Ray focusing at 45 degrees on the lateral side, the same way we do for lumbar ureteric stones.

So we didn’t modify the lithotriptor, the source of shock wave is the same, all the other
components are unchanged and the installing of this 2 components is made easily, without affecting the structure of the lithotripter. More than that, the movements of the table are ideal for an optimal triggering of the stone with no bone structure in the path of the shock waves ready to disperse them.

This invention, even as it is, not yet registered as a trade mark, has successfully extend the indications for ESWL for stones in the distal part of the ureter and, moreover, for the Steinstrasse, a complication occurred in treating larger stones (more than 1.5 - 2 cm). Yet, it remains ideal for symptomatic small stones 0.6 - 0.7 cm located in the uretero-bladder junction.

The first trial for this inventions and its success rate was published in the Romanian Journal of Urology, in 1994, and we were very glad to inform that our success rate was the same with the rate reported by the urologist using special lithotriptors designed from the beginning for this stone localization [1]. Beyond the professional satisfaction that I have discovered something new, there is the enthusiasm of helping patients in avoiding the possible complications of open surgery. Keeping in mind this is a pathology with a high grade of recurrence for a lot of patients, especially young.

Using this second generation lithotripter, I started to put the patient in a special position and with a special compression during the procedure I started to perform ESWL even for stones migrated into the lumbar ureter, a fact which was not mentioned in the books for this type of machine. I have made the first try for slim patients with abdominal circumference less than 90 cm for man and 80 cm for woman. The good results observed encouraged me to continue this strategy for more obese patients and the results were good enough to continue doing ESWL for lumbar ureteric stones with a special compression produced by a radiolucent textile device. We can observe two big advantages:

1. Bringing the stone in the F2 area of the lithotripter, so ESWL has become a standard procedure and the first line treatment for lumbar ureteric stones at a time when we did not have the semirigide ureteroscope to use as an alternative for ureteric stones. The only option was open ureterolithotomy, an intervention with many risks and complications; Thinking that many young patients with a possible relapse in few years have been successfully treated, I consider this extension of the indications with our KS088-4 machine a very good opportunity.

2. The special compression had already succeeded in limiting the respiratory movements during the procedure, despite an initial patient discomfort at the beginning of the procedure, with a good impact on the number of shock waves targeting the stone and, of course, with a better fragmentation rate.

I had noticed the benefits of the new compression system when we have compared the results between the groups with and without compression. Anyway, a lot of patients avoided the classic open surgery and this is one of the most important results in my career as ESWL supervisor.

The efforts and the progress we have achieved in this field were recognized by the Ministry of Health with an Official Certificate for Training young urologist in the field of ESWL, one of only five centers in Romania with this important recognition.
THE DIDACTIC ACTIVITY

Since 1991, I have been continuously working as a lector in the Urology Department of the "Grigore T. Popa" University of Medicine and Pharmacy. I’ve always had a high level of didactic responsibility (regular and supplementary hours). Therefore, I’ve had the direct responsibility for the theoretical and practical preparation of a large number of students, during classes and clinical rotations. I tried to impose a high level to these activities, always emphasizing the importance of urology in the professional development of the contemporary doctor. I’ve always adapted my activity, in order to fulfill the analytical programme. I have evaluated the students through multiple methods (discussions, written tests, multiple-choice tests) with a rigorous and correct grading.

I’ve permanently contributed to the organization and development of the didactic activity in the Urology Department through: elaboration of original materials: course books, clinical rotation guide for the Romanian, English, and French programme, presentation of medical movies made by me or by my colleagues in other Urology clinics throughout the country or abroad, guidance for my less-experienced colleagues, information-gathering upon the actual tendencies in the urological educational system.

As a lecturer, I was in charge of the course in the Healthcare Assistant Programme in Iasi and branches in Botosani and Bacau. The lectures comprised information from the urology books, with novelties accepted in the specialized literature, with well-represented graphic illustrations.

As Associated Professor and Coordinator of the Didactic activity in the Urology Department of the "Gr.T. Popa" University of Medicine and Pharmacy, I guided different teams engaged in elaborating didactic material (course books): Clinical Urology ("Gr.T. Popa" Editure, Iași, 2016), Images from the urological practice ("Gr.T. Popa” Editure, Iași, 2014), Urologie Pratique (Pim Editure, 2016).

As a result of my didactic experience accumulated in the Urology Department, I have elaborated didactic materials as first or second author.

I introduced courses on new directions, according to the modern tendencies of the international medical education, through the e-Mediqual Project (European Quality and Professional Competence in Medical University Education and Management. Project POSDRU 63815/2009).

In my following didactic career, I intend to:
- introduce integrative courses on new directions, both as optional and compulsory classes, according to the curriculum requests of our university;
- introduce in the clinical rotations for students the modern study techniques, my present images from the operating room or with endourological procedures and medical movies as well;
- create practical books for the English and French programme, in order to help the students to get accustomed to the right approach for an urologic patient, by presenting the right way to talk to a suffering person, as I believe this is an essential condition for an efficient medical action. At the same time, this book should be useful for our residents that might want to follow a clinical traineeship in an English-speaking country.
EDUCATIONAL ACTIVITIES

I took part in the elaboration and execution of grants/project, in multidisciplinary team coordination, and in organizational management as well.

I initiated, elaborated and implemented research projects/interdisciplinary development projects, that had and continue to have as a purpose the development and the increase in the quality of the medical act.

The communication skills, both in group and individual, and the interactive interpersonal communication were gained through medical practice, professional development, research partnership, and during the didactic activity as Associated Professor, and afterwards as Professor.

I have also worked in various professional environments (medical practice, university). Therefore, I can summarize the main aspects of my activity, as follows: excellent level in education (university and post-university) and research, in an increasingly competitive environment, through the development of the didactic methods and interdisciplinary research in urology. This objective will be acquired through the integration in the educational and research process of the knowledge and methods specific to the following departments: urology, nephrology, nutrition diseases and diabetes, infectious diseases.

Other objective are:

- An integrative educational curriculum at the highest of standards, for the urology course, designed for the medical students/health care assistants and for the residents from different specialties undertaking medical traineeship in our clinic;
- Coordination of innovative bachelor thesis in urology, through a complex interdisciplinary view;
- Setting of new courses;
- The finalization of the habilitation thesis, which will enable the coordination of PhD thesis either in urology or in connected specialties with borderline subjects. Another objective of my didactic activity is the improvement of teacher/student communication. I see this as the essential premise for the improvement of the educational process as a whole. By using questionnaires, I think we can find out the main difficulties regarding the educational system, and also the best solutions to overcome them.

I also intend to improve the communication with the students that are interested to take part in the Erasmus Programme, or who are already involved, as I am the Erasmus coordinator in our University. Our students that leave for other European medical centers, and the incomings as well, must be seen as the best ambassadors of the medical school in Iași and Romania, and that’s why we should put our efforts in this programme accordingly.
II. SCIENTIFIC, PROFESSIONAL AND ACADEMIC ACHIEVEMENTS

In the following pages I will present the main research topics and make a brief summary of the main articles I have published with my colleagues.

II.1. URINARY STONES

Kidney stones are concretions of minerals formed in the kidneys. In the last 30 years, we have seen that in western countries the incidence of stone formers is growing, mainly in the oxalocalcic type. In the same period of time, there have been made important progresses in the new spectacular technologies to treat urolithiasis (stones originating anywhere in the urinary system, including kidney and bladder). The male/female ratio in this pathology is “favorable” to men (~3/1) and the peak of diagnostic is between 40 and 49 for man and 30-39 for women. There is no scientific connection between heredity and the sex of the patient: we know there is a familial component (probably polygenic) with variable penetrance, including a genetic predisposition of stone formers.

The real incidence of new cases in urolithiasis is underestimated, because many patients are treated by the general practitioner without admission to the hospital for rigorous investigation. In the western world 5 - 10% of the population will have at least one episode of renal colic during their lifetime.

It is possible to individualize three “profiles” of kidney stones:
- those which can be eliminated spontaneously or with the help of so-called “minimally aggressive” Extracorporeal Shock Wave Lithotripsy (ESWL), retrograde ureteroscopy (RURS);
- those that need more aggressive methods of treatment (PCNL – percutaneous nephrolithotomy or classic open surgery);
- those which can destroy the kidney and determine the urologist to perform nephrectomy.

Principles of lithogenesis:
In most of the cases, the formation of a stone is the result of 5 consecutive phases:
1. Oversaturation: crystals ± tubular destroyed cells, produced by trauma or infection, make the initial support of crystallization (heterogenic nucleation). The urinary flow and the natural crystallization inhibitors, like citrate, play a very important role in preventing the appearance of these crystallization nucleus;
2. Secondary aggregation and growing of these crystals, which can no longer be evacuated from the kidney;
3. The crystals get stuck in the tubular walls or on mucoproteic material;
4. The retention of the stone at the papillary level (Randall’s plaque) or on the tubular scars;
5. The growing of the stone: the initial “aggregate” will attract new crystals in concretion with the composition of urine.
Normal urine contains inhibitors of stone formation such as:
- Citrate - inhibits the nucleation, growth and aggregation of calcium containing crystals;
- Calgranulin (calcium binding protein);
- Tamm-Horsfall protein;
- Glycosaminoglycans;
- Uropontin;
- Nephrocalcin, etc.

The biochemical mechanism of action of these substances has not yet been thoroughly elucidated. However, when these substances fall below their normal levels, stones can form out of an aggregation of crystals.

We must understand that kidney stones often result from a combination of factors. They are more common in people whose diet is based on animal protein, salt, sweets, and/or do not consume enough water or calcium.

Classifications of the stones can be done according to the following criteria:
- stone size (in mm);
- stone location - upper, middle and lower calyx, renal pelvis, upper (or lumbar) ureter, middle (iliac) ureter or distal (pelvic) ureteric stone, bladder stones;
- stone X-ray characteristics - According to the appearance on plain X-ray (KUB) (Table 1.):

<table>
<thead>
<tr>
<th>Radiolucent</th>
<th>Poorly radioopaque</th>
<th>Radioopaque</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric acid</td>
<td>Magnesium ammonium phosphate</td>
<td>Calcium oxalate dehydrate</td>
</tr>
<tr>
<td>Ammonium urate</td>
<td>Apatite</td>
<td>Calcium oxalate monohydrate</td>
</tr>
<tr>
<td>Xantine</td>
<td>Cystine</td>
<td>Calcium phosphate</td>
</tr>
<tr>
<td>“Drug” stones</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 1. Stone X-Ray characteristics**

**Etiology of stone formation:**
- non-infection stones: calcium oxalate and phosphate, uric acid;
- infection stones: magnesium-ammonium-phosphate, apatite, ammonium urate;
- genetic causes: cystine, xanthine;
- “drug” stones.

Urolithiasis presents specific interest for both patient and doctor because of the risk of recurrence (about 50% of recurrent stone formers have just one recurrence during their lifetime). For high risk stone formers there are:
1) general factors (familial stone formation, early onset of urolithiasis, infection stones, solitary kidney, uric acid, calcium hydrogen phosphate);
2) diseases associated with stone formation (hyperparathyroidism, sarcoidosis, gastrointestinal disorders) ± osteoporosis (?);
3) genetically determined stone formation (cystinuria, primary hyperoxaluria, xanthinuria, renal tubular acidosis, etc.);
4) anatomic abnormalities associated with stone formation (medullar sponge kidney, horseshoe kidney, ureteropelvic junction obstruction, ureterocele, caliceal diverticulum, vesico-uretero-renal-reflux, etc.).
Clinical signs:

There is no correlation between the size of a stone and the clinical/psychopathological consequences: a small stone (4-5 mm) can suddenly become totally obstructive with acute severe pain, and a staghorn stone can be asymptomatic for years.

Renal colic is a pain correlated with a sudden rise of pressure in the renal pelvis and calyx due to an acute obstruction made by the migrating stone in the ureteropelvic junction or ureter. If the obstruction is progressive, the patient will feel a dull lumbar pain.

The renal colic has four clinical elements which will help the doctor recognize it easily:
- the pain comes suddenly (only in very rare cases with a sensation of weakness/dull lumbar pain);
- the pain is located unilaterally in the lumbar area;
- the irradiation of pain is typical from the lumbar region down to flank, bladder or testicles (following the ureteral tract);
- the evolution of the pain is paroxystic, with very painful periods followed by more or less normal times.

Other signs can be:
- agitation, the patient cannot settle into a position "without pain";
- the digestive signs - sometimes more visible than pain: nausea, vomiting;
- urinary signs: polakuria and the sensation that the bladder is always full when the stone is arriving at the ureteral-bladder junction;
- in patients with fever or solitary kidney, and when the diagnosis of stone is doubtful, immediate imaging is indicated.

The renal colic is opposed to non-colic type pain, such as the one associated with appendicitis or pancreatitis, in which movements causes increased pain to the patient, so that he holds very still.

Males may complain of pain in the testicle or scrotum. The patient cannot find a comfortable position and often writhes or paces with pain.

Blood may or may not be visible in the urine, because the stone has irritated the kidney or the ureter.

Diagnostic:

Patients with renal stone disease usually display the symptoms mentioned above (but they can also be asymptomatic!). The clinical diagnosis should be supported by an appropriate imaging investigation:

a) Ultrasound should be the first procedure, because it can identify stones located in the calices, pelvis, lumbar ureter and the ureteric-bladder junction, the consequences of the stones (uretero-) hydronephrosis, the status of the renal parenchyma. Do not forget that this is an inexpensive, safe and reproducible investigation for urinary stone detection. For renal stones > 5mm, the sensitivity is ~ 96% and the specificity ~ 100%.

b) KUB can detect radiopaque images in the area of the uretero-pyelo-calyceal system. It helps in making the difference between radiolucent and radiopaque stones, and in the follow-up after different procedures (PCNL, ESWL etc.). The sensitivity of KUB is 44 - 77% and the specificity is ~85%.

c) IVU (intravenous urography), performed after KUB, was the gold standard for the diagnostic of urolithiasis for many years;

This investigation offered good and specific information on the position of the stone(s), (uretero-) hydronephrosis, renal function and on the strategy to follow.
It was replaced by non-contrast enhanced CT (NCCT), which is now the standard method for acute flank pain.

NCCT has the advantage to measure the stone density and the skin to stone distance (important for ESWL indications in obese patients). The big disadvantage is that with this investigation we do not have information about the renal function or anatomy of the collecting system; the actual recommendation for planning treatment for renal stone is to do a renal contrast study (enhanced CT or IVU).

The basic laboratory analyses we must recommend to a patient with urolithiasis (first episode) are:
1. Urine:
   - urinary sediment (red cells, white cells, nitrite, pH);
   - urine culture.
2. Blood:
   - serum blood sample (creatinine, uric acid, calcium, sodium, potassium);
   - blood cell count;
   - CRP (C reactive protein).

If an intervention is needed, we must check the PTT or INR coagulation test (PTT = partial tromboplastin time; INR = international normalized ratio).

The patients with high risk for stone recurrence should undergo a specific investigational programme.

\[d)\] Retrograde pyelogram is the radiological procedure where the contrast agent is injected on the ureteral stent inserted with the help of cystoscope. We can see the radiolucent stones in the ureter and pelvic system. While a retrograde pyelogram is the most reliable method for visualizing the urinary system (mainly in silent kidney on IVU), it is generally used only where other imaging methods are inadequate or unsuccessful. The diagnosis of renal stone disease involves a medical history, physical examination, laboratory evaluation and imaging tests.

The complex metabolic evaluation of a patient is necessary when the risk of recurrence is important.

*Treatment of renal colic:*

The first choice should be non-steroidal anti-inflammatory drugs (NSAIDs): Xeforapide (Lornoxicam) 1vial x 2/day, Diclofenac 1 ampule x 2/day, Ketrarol 1 ampule x 3-4/day; they prove effective in the relief of pain (in lithiasic patients pain relief should be initiated immediately!).

Although NSAIDs can affect renal function in patients with an already reduced renal function, it has no effect on renal function in normal kidneys. The action mechanism is the inhibition of the synthesis of prostaglandin G2, considered to be the key factor in renal colic. The second choice are opioid drugs (Tramadol). They are less effective than NSAIDs, and the adverse effects rate is more significant (nausea, vomiting).

Alpha-blocking agents, administered on a daily basis, also reduce recurrent colic (Tamsulosin 1tb/day).

When NSAIDs or opioids cannot be used, we can try spasmolytics as an alternative (No-Spa-drotaverine 2tbs x 3/day or 2/day) but often efficiency is lower.
In those specific cases when pain relief cannot be obtained through the drugs mentioned, a double J stent insertion (or nephrostomy!) should be carried out. Endourological treatment (a double J stent insertion or nephrostomy!) is also needed in following situation: renal colic + fever (sepsis), renal colic associated with a single kidney (surgical, congenital, functional); renal colic + hematuria.

**Treatment of the stone:**
The strategy of treatment will be decided after ultrasound, KUB, IVU/CT and blood, urine analyses.

**Medical expulsive therapy:**
This is a solution for many patients with small stones (3-5 mm in diameter). Medical expulsive therapy should only be used in patients who are reasonably comfortable with this treatment and no active stone removal is indicated.

Selective alpha-blockers (Tamsulosin, Silodosin) have proved to be helpful in increasing stone expulsion rate. Also, calcium channel blockers (Nifedipine) have been shown to have a similar effect. These medications must be "helped" with increased water intake. Several studies have shown that medical expulsive therapy also has an expulsive effect on proximal ureteral stones, and after ESWL (for ureteral or renal stones) it seems to expedite and increase stone-free rates.

**Chemolytic dissolution of stones:**
Specific stones can be dissolved by oral or percutaneous irrigation: Ammonium-Magnesium-Phosphate, Carbon apatite, Cystine, Uric acid, Brushite. Oral chemolysis is efficient only for the uric acid calculi: alkaline citrate Uralyt-U. When chemolitolysis is planned the pH must be adjusted (7 - 7.2). Additional treatment with allopurinol may support the chemolysis and prevent the recurrent stones.

The percutaneous irrigation chemolysis can be done with 10% hemiacitrin solution for infection stones (struvite, carbon apatite and brushite). The treatment algorithm for lower pole calculi depends on the stone size and on the anatomical condition (PCNL, retrograde FLEXIBLE URS).

**Table 1. Treatment options for ureteric stone**

<table>
<thead>
<tr>
<th>Ureteral stone</th>
<th>Ca Ox</th>
<th>Uric acid stone</th>
<th>Infected stone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal</td>
<td>ESWL / URS</td>
<td>JJ + oral</td>
<td>Antibiotics + ESWL</td>
</tr>
<tr>
<td>Middle</td>
<td>ESWL / URS</td>
<td>ESWL / URS</td>
<td>Antibiotics + ESWL</td>
</tr>
<tr>
<td>Distal</td>
<td>ESWL / URS</td>
<td>ESWL / URS</td>
<td>ESWL</td>
</tr>
</tbody>
</table>

**Modern procedures in urolithiasis:**

Extracorporeal Shock Wave Lithotripsy (ESWL):
ESWL is a relatively new procedure which uses shock waves produced outside the body to break a kidney/ureteric stone into small pieces that can travel more easily through the urinary tract and pass through.
This minimally invasive procedure is generally painless (with the new machines) and is usually conducted on an outpatient basis, without need for anesthesia.

ESWL is accomplished through the use of the lithotripter, a device that emits shockwaves initiated in an electrohydraulic, piezoelectric or electromagnetic generator. The shockwaves produced outside the patient are focused to the stone. They go through the skin and all the layers of the abdomen wall and discharge the energy at the interface between stone and urine.

During ESWL treatment, the patient reclines on the machine bed, which has a water-filled back support.

ESWL can remove more than 90% of stones in adults. The success rate for ESWL depends on the efficacy of the lithotripter and upon the following factors: size, location of the stone, composition (hardness of the stone).

Contraindications: pregnancy, bleeding, diathesis, uncontrolled urinary tract infections, severe skeletal malformations and severe obesity, arterial aneurysm in the vicinity of the stone treated, anatomical obstruction distal of the stone. Many patients with intense renal colic due to an obstructing ureteric stone are first treated with a double J insertion on that side. Recent studies reported that routine use of internal stents before ESWL does not improve the outcome in terms of stone fragmentation rates both for renal or ureteric stones.

The advantage of ESWL is that the sessions can be repeated (within one day, in the case of ureteral stones), but there is no consensus on the intervals required between repeated ESWL sessions for kidney stones.

In the case of infected stones or bacteriuria, antibiotics should be administered before ESWL and continued at least four days after treatment. ESWL-related complications are rare, the most frequent complication is renal-colic in 2-4% followed by urinary tract infections or sepsis occurring in 1-2% of cases. Other very rare complications: renal hematomas, liver/spleen hematoma, bowel perforation, cardiac dysrhythmia.

Retrograde ureteroscopy (URS):

Retrograde ureteroscopy is a routine procedure performed by urologists. The most common indication is to treat urinary tract calculi, particularly those that are either unsuitable for ESWL or are refractory to that form of treatment.

Other indications include:
- Evaluation of the abnormal lesions/tumors revealed by IVU or retrograde pyelography (can include the biopsy of the lesion);
- Unilateral essential haematuria;
- Evaluation of a ureteral injury.

The therapeutic indications are (besides ureteric stones):

- Ureteric stenosis;
- Ureteropelvic junction stenosis;
- Superficial ureteric tumors;
- Extraction of foreign bodies (fragments of a stent);
- Rachi-/general anesthesia can be used.

Intraoperative incidents can be: bleeding, the impossibility to introduce the ureteroscope in the ureter or to advance at the stone, ureteral lesion, perforation of ureter, ureteral avulsion.
Complications can be: urinary tract infection, urosepsis, ureteral orifice stenosis, ureteral stenosis, bladder ureteric reflux, renal colic.

Contraindications are related to untreated urinary tract infections and uncorrected bleeding diathesis prior to therapeutic endoscopy, pregnancy, etc.

Percutaneous nephrolithotomy (PCNL):

PCNL is a procedure for removing medium size or larger renal calculi by means of a nephroscope passed into the kidney through a track created in the lumbar area. This is a much more elegant therapeutic option than open surgery (pyelolithotomy), and can treat most of the staghorn stones in functional kidneys.

A standard PCNL is performed under rachi-/general anesthesia. The first step is puncture under ultrasound guidance in the inferior calyx, in which we insert a guide-wire. Coaxial Teflon dilatations are used to create a tunnel from skin to renal pelvis in order to insert the nephroscope (an instrument with an optic fiber light source and two additional channels for viewing the inside of the kidney and irrigating the system. The stones are broken up with an ultrasonic, electrohydraulic probe (Swiss Lithoclast), or a holmium laser. The small stone fragments can be extracted directly through the nephroscope. At the end, a nephrostomy tube is placed in order to carry the fluids from the kidney into the drainage bag.

A newer form of PCNL called mini-percutaneous nephrolithotomy (MPCNL) can be performed with a miniaturized nephroscope (it has the advantage of fewer complications, short operation time and shorter recovery of the patient).

PCNL has a high success rate of stone removal (~ 98%), this goal is even achieved in 2 or 3 interventions (during the same hospitalization). If at the end the urologist cannot extract all the stones/fragments due to anatomical/technical conditions, sessions of EWSL can be performed afterwards.

Complications of PCNL:
- Perforation of the renal pelvis;
- Bleeding: injury of blood vessels within the kidney, as well as from blood vessels in the area of incision. About 20% of patients scheduled for PCNL require a blood transfusion during the procedure with 2.8% requiring treatment for bleeding after procedure;
- Infection, fever, formation of arteriovenous fistula;
- Injury of surrounding organs (damage to the spleen, liver, lung, pancreas, goal bladder, colon – in rare cases). Standard PCNL has a higher rate of complications than ESWL, but it is more successful in removing calculi.

Ultrasonic, ballistic and Ho Yag laser devices are recommended for intracorporeal lithotripsy using a rigid nephroscope. When using flexible instruments, the Ho YAG laser is currently the most effective device available.

Contraindications of PCNL:
- All bleeding disorders;
- Untreated urinary tract infections;
- Atypical bowel interposition;
- Tumor in the presumption access tractarea;
- Potential malignant tumor of the kidney;
- Pregnancy.
Open surgery in reno-ureteral stones:

Advances in ESWL and endourological procedures (PCNL, URS) have resulted in a significant decrease in the indications for open stone surgery (1.5% of all stone removal interventions in developed countries).

Indications: complex stone burden, treatment failure (ESWL/PCNL or URS), morbid obesity, skeletal deformity, concomitant open surgery, non-functional lower pole (partial nephrectomy), non-functioning kidney (nephrectomy), patient choice. Pyelolithotomy (extraction of the stone through a pelvic incision) and ureterolithotomy (extraction of the stone from ureter) is now replaced by laparoscopic procedures in certain situations.

The laparoscopic approach is associated with a lower post-operative morbidity, shorter hospital stay and better cosmetic results.

II.1.1 DESMOPRESIN IN THE TREATMENT OF RENAL COLIC

In the large field of research for kidney stones I would like to mention the study: 


The paper tried to give an answer to this problem starting from the physiopathology of renal colic: obstruction of the ureter induce an important secretion of E2 prostaglandines with the increase of renal blood flow and diuresis, making the intrapelvic pressure bigger and an aggravating of the intensity of the pain.

Renal colic is a very frequent and severe complication of kidney stones [2]. The acute dilation and stretching caused by ureteral obstruction is accompanied by excruciating pain [3]. The increase in hydrostatic pressure in the renal pelvis triggers prostaglandin secretion, causing a raise in the renal blood flow and diuresis [3]. This phenomenon leads to further increase in ureteropelvic pressure and ureteral contractility, with an aggravation of pain in a vicious circle, until eventual stone elimination [3].

The only two medications currently used for the therapy of acute renal colic are nonsteroidal anti-inflammatory drugs (NSAIDs), which are potent inhibitors of prostaglandin synthesis, and opioids, decreasing pain via central effects [2, 4]. The analgesic efficacy of such drugs is, however, highly variable, with many individual cases resistant to therapy [5]. These drugs are, moreover, not devoid of side effects. NSAIDs may aggravate renal insufficiency, cause gastroduodenal ulcerations and increase the risk of stroke, whereas opioids are addictive and may cause nausea, vomiting, respiratory distress, drowsiness or impaired consciousness [6, 7]. Therapeutic alternatives to the existent drugs are therefore needed.

Arginine vasopressin (AVP) or antidiuretic hormone is known as a major regulator of water balance by stimulating water reabsorption in the distal and collecting tubes [8].

Beside their direct effects, prostaglandins also antagonize the renal action of AVP, by interfering with cyclic adenosine monophosphate-mediated signals, thereby further increasing diuresis and pain [8-11]. Therapy with prostaglandin synthesis inhibitors seems, moreover, to be more efficient in reducing the pain of renal colic in patients having higher levels of circulating AVP; in experimental models of acute obstruction, desmopressin reduces ureteral pressure and pain [12].
Desmopressin also exerts direct myorelaxant effects on the smooth muscles of rabbit renal pelvis [13]. The central V1a receptor or AVP may be involved in the perception of pain [14]. All these data support the use of AVP analogues in the therapy of lithiasic renal colic [10, 15].

1-Desamino-8-d-arginine vasopressin (desmopressin) is a synthetic structural analogue of AVP with potent, long-lasting antidiuretic effect, but reduced vasopressor activity. The intranasal form of administration was tested in the therapy of renal colic, with variable results [10, 15–21]. Intranasal desmopressin was proposed by certain authors as an efficient analgesic in monotherapy or as an adjuvant for NSAIDs [10, 15–19], whereas others did not indicate any significant beneficial effects of intranasal desmopressin in monotherapy [20] or in combination with NSAIDs or opioids [20, 21]. The sublingual administration form of desmopressin was recently used in renal colic, but only in combination with morphine, and not in monotherapy or combined with NSAIDs[22]. Desmopressin is not licensed for use in renal colic, nor included in treatment guidelines; it is often used off-label in clinical practice for pain relief in renal colic, alone or as adjuvant therapy [23]. The aim of our study was therefore to test the efficacy of sublingual desmopressin (Minirin Melt) in the therapy of renal colic, alone or in combination with a NSAID.

We performed a single-blind randomized prospective multicentric study, enrolling patients in the emergency units of two Romanian University Hospitals (Iasi and Targu Mures) during a period of 2 years. The study was performed according to the Declaration of Helsinki (revised, Edinburgh, 2000). All applicable regulatory requirements and local independent Ethics Committee approvals of the two Universities were obtained before enrolling patients.

An informed, written consent was obtained from all enrolled patients. We recruited an initial number of 249 patients (167 males and 82 females between 18 and 82 years, mean age of 42.6 ± 13.5 years) with renal colic of lithiasis etiology and who did not receive any medication previously.

Exclusion criteria consisted in the presence of fever, renal insufficiency, hyponatremia, congenital hydronephrosis, renal tumors, pregnancy, endourologic emergencies (e.g.: obstructive anuria), active peptic ulcer disease, severe cardiovascular ischemic disease, hemorrhagic diathesis. The presence of kidney stones was confirmed by radiological and ultrasound investigation. After signing the informed consent, the patients were randomly assigned to four groups. Group NSAID (71 patients) received ketorolac tromethamine (ketorolac) 30 mg intramuscular (im) and sublingual (sl) placebo (vitamin C), groups D1 and D2 (57 and 62 patients respectively) received 60 or 120 μg sl desmopressin (Minirin Melt), and group C (59 patients) received a combination of 60 μg sl desmopressin and 30 mg im ketorolac. Randomization was made successively in the four groups in the rigorous order of address-ability to the two emergency units, until reaching a total number of 50 volunteers experiencing a decrease in the VAS in each group 30 min after therapy administration.

The intensity of pain was assessed by the patients with a visual analogue scale (VAS) ranging from 0 (no pain) to 10 (unbearable pain) at admission and 30 min after therapy administration [24]. When pain intensity increased despite therapy, becoming unbearable or remaining at initial, unbearable levels, patients were administered opioids (tramadol) and/or underwent emergency urological intervention (insertion of a double J ureteral probe for facilitating the drainage) and were dropped out from the study. Patients were monitored for therapy-related side effects. Blood pressure was measured in all volunteers before and 30 min after therapy.
administration. Serum osmolarity and creatinine were assessed in all patients receiving desmopressin before and 30 min after drug administration. The characteristics of study groups and the number of aggravated patients dropped out from the study are shown in Table 1. Blood pressure values, serum sodium and creatinine before and 30 min after therapy are shown in Table 2, expressed as mean ± standard deviation.

**Table 1. Characteristics of study group**

<table>
<thead>
<tr>
<th>Group</th>
<th>Therapy</th>
<th>Mean age ± SD</th>
<th>Number</th>
<th>Dropouts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>M</td>
<td>Total</td>
</tr>
<tr>
<td>NSAID</td>
<td>Ketorolac 30 mg im</td>
<td>42.5 ± 13.4</td>
<td>24</td>
<td>47</td>
</tr>
<tr>
<td>D1</td>
<td>Minirin Melt 60 µg sl</td>
<td>41.8 ± 11</td>
<td>19</td>
<td>38</td>
</tr>
<tr>
<td>D2</td>
<td>Minirin Melt 120 µg sl</td>
<td>43.1 ± 14.1</td>
<td>21</td>
<td>41</td>
</tr>
<tr>
<td>C</td>
<td>Minirin Melt 60 µg + Ketorolac</td>
<td>42.7 ± 14.6</td>
<td>18</td>
<td>41</td>
</tr>
</tbody>
</table>

**Table 2. Biological parameters before and 30 min after therapy**

<table>
<thead>
<tr>
<th>Group</th>
<th>Blood pressure (mm Hg)</th>
<th>Serum Na (mEq/L)</th>
<th>Serum creatinine (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0'</td>
<td>30'</td>
<td>0'</td>
</tr>
<tr>
<td>NSAID</td>
<td>130 ± 17</td>
<td>126 ± 18</td>
<td>77 ± 12</td>
</tr>
<tr>
<td>D1</td>
<td>129 ± 19</td>
<td>127 ± 16</td>
<td>79 ± 11</td>
</tr>
<tr>
<td>D2</td>
<td>130 ± 22</td>
<td>125 ± 20</td>
<td>76 ± 11</td>
</tr>
<tr>
<td>C</td>
<td>132 ± 23</td>
<td>127 ± 18</td>
<td>80 ± 9</td>
</tr>
<tr>
<td>All</td>
<td>131 ± 18</td>
<td>126 ± 16</td>
<td>78 ± 9</td>
</tr>
</tbody>
</table>

Mean age and sex distribution were not significantly different in the four treatment groups (Table 1.). The incidence of dropouts (patients with aggravating pain despite therapy) was significantly higher in the NSAID group receiving ketorolac and sublingual placebo than in all the other groups that received sublingual desmopressin either alone or in combination with ketorolac (Fig. 1). Two patients treated with ketorolac in monotherapy and one patient treated with combination therapy, but no patients treated with desmopressin in monotherapy experienced mild epigastric discomfort, possibly related to NSAID administration. Mean blood pressure of all patients was of 131/78 mmHg at admission and 126/74 mmHg at 30 minutes after therapy, without significant differences among groups (Table 2). All volunteers enrolled in the study and receiving sublingual desmopressin had normal serum sodium and creatinine 30 min after drug administration, irrespective of their age or sex, with unmodified mean values. The normality of these parameters 30 min after drug administration suggested therapeutic safety of sublingual desmopressin given once for renal colic (Table 2).
Fig. 1. Mean pain score ± SEM (visual analogue scale) at admission and 30 min after therapy.

Mean pain intensity evaluated by the VAS in patients kept in the study until the end was high and comparable at admission in all groups, pleading in favor of study homogeneity (Fig. 1.). All therapies significantly decreased pain intensity after 30 min (Fig. 1.). The higher dose of desmopressin (group D2) decreased absolute pain intensity significantly more than ketorolac alone (group NSAID, Fig. 1. left). The combination of 60 μg sl desmopressin and ketorolac (group C) was significantly more efficient in decreasing absolute pain intensity than any of the two drugs in monotherapy (groups NSAID and D1, Fig. 2. right). Correspondingly, combination therapy of 60 μg sl desmopressin and ketorolac (group C) caused a significantly higher relative reduction in the VAS (percentage from initial) than any of the two drugs in monotherapy (groups NSAID and D1, Fig. 2.).

Fig. 2. Mean pain score decrease ± SEM (% from initial pain score evaluated by the visual analogue scale) in the treated patients.
Our clinical study is one of the first aiming to follow the effects of sublingual desmopressin in lithiasic renal colic. The two chosen doses of sublingual desmopressin were in the range of the intranasal administration doses used in previous studies. Evaluation endpoint was located at 30 min after therapy administration, in line with other clinical studies [10-12, 16–22]. We decided to include only two VAS evaluations for simplifying the protocol and increasing volunteer adherence. Compared to other reports, our investigation conferred several advantages and novelties. First of all, the number of enrolled patients was larger. Secondly, the study included a control group, treated with a NSAID, and groups treated with sublingual desmopressin in monotherapy or in combination with a NSAID. The study design allowed therefore a head-to-head comparison of the therapeutic efficacy of two different drugs in monotherapy or in combination.

Intranasal desmopressin given in monotherapy has somehow limited analgesic effects in renal colic [10, 15], being considered less efficient than NSAIDs or opioids and merely playing an adjuvant role [16, 20, 21]. In contrast, we found sublingual desmopressin (Minirin Melt) at least or even more efficient than a classical NSAID (ketorolac) in treating lithiasic renal colic. The number of therapeutic failures was significantly higher in the NSAID treated group than in the groups treated with sublingual desmopressin, irrespective of dosage (Fig. 1.). Moreover, sublingual desmopressin decreased pain intensity evaluated by the VAS in the responsive patients to a level comparable to that attained by the therapy with NSAID, either in absolute values (Fig. 2.) or as percentage from the initial pain score, with the higher dose of 120 μg Minirin Melt being more efficient than ketorolac 30 mg im. The far greater number of patient dropouts before 30 min in the group treated with ketorolac alone and, the exclusion of dropouts from the study, suggests an even more important difference in therapeutic efficacy in favor of desmopressin.

It is not immediately clear why desmopressin was more efficient for treating renal colic in our study compared to others, but the difference seems to reside in the way of administration. Therapeutic intervention was generally prompt after the onset of renal colic and sublingual desmopressin is known to be more readily available in the general circulation than other forms of administration. Our data is also more consistent than previous clinical studies, taking into consideration the higher number of enrolled patients. Importantly, although epidemiological reports suggest a risk of hyponatremia and water intoxication associated with chronic desmopressin use, one dose of sublingual desmopressin was not accompanied by the above-mentioned side effects in our study (Table 1.). We did not observe any clinical signs of hyponatremia in our volunteers, and serum sodium evaluated at the end of the follow-up was unmodified in patients receiving one dose of sublingual desmopressin, including the nine volunteers of over 70 years of age. NSAID administration caused gastric discomfort in a few patients. Furthermore, therapy with sublingual desmopressin did not imply supplementary water ingestion, such as for oral NSAID therapy, decreasing the risk of further basinetral distension or drug elimination through vomiting.

We further wanted to check whether patients with lithiasic renal colic may benefit from a combination therapy between NSAIDs and sublingual desmopressin. This type of combination seems logical, since the two drugs act on renal hydrodynamics through different mechanisms of action. Desmopressin lowers ureteral pressure by increasing water reabsorption [12], whereas NSAIDs inhibit local prostaglandin secretion, thereby decreasing local blood low and ureteral contractility. The inhibition of prostaglandins may also increase
desmopressin efficacy by increasing local cAMP production [9, 10, 15, 16]. Another argument in favor of the administration of drug combination is that higher AVP levels seem to increase the sensitivity of renal colic to NSAID therapy [11]. Other authors already tested the efficacy of combination therapy between intranasal desmopressin and a NSAID in renal colic. Certain authors observed additive effects [16, 17, 19], whereas others did not notice any benefit of combination therapy [20].

Our study showed mild but statistically significant additive analgesic effects after 30 min of follow-up when the lower dose of desmopressin (60 μg Minirin Melt) was added to ketorolac (group C, Fig. 2.), suggesting possible supplementary beneficial effects of this drug combination. The benefit of combination therapy seems, however, to be limited to a difference of 1.5 points in the VAS (Fig. 1.). Further studies with a longer follow-up period may be more informative regarding therapeutic efficacy. Sublingual desmopressin was recently used in the therapy of lithiasic renal colic in combination with morphine [22]. The authors suggested that desmopressin is not beneficial in this combination and may even decrease the central analgesic effects of opioids. The presence of arginine vasopressin receptors in brain is abundant [14], and this type of interference with opioid central effects may be possible, although further studies are needed, especially since it is known that desmopressin does not pass through blood-brain barrier. The study did not include, however, a group treated with sublingual desmopressin in monotherapy. The absence of initial evaluation of pain intensity before therapy administration is another major drawback of this study.

II.1.2 PARTICULARITIES OF BONE METABOLISM AND CALCIUM REGULATORS IN YOUNG PATIENTS WITH RECURRANT STONE EPISODES

I have tried to investigate, in a grant sponsored by the University of Medicine and Pharmacy Iasi, different aspects of the metabolic aspects connected with the recurrent kidney stones, the conclusions being presented in an article: PARTICULARITIES OF BONE METABOLISM AND CALCIUM REGULATORS IN A GROUP OF YOUNG MALES WITH IDIOPATHIC HYPERCALCIURIA AND RELAPSING LITHIASIS, published in Acta Endocrinologica. Vol. X No 2, April - June 2014.

We have started this study from the unanimous recognized fact that idiopathic hypercalciuria is a risk factor for kidney stones and in many patients hypercalciuria is associated with with a low bone density, but these relations were not fully understood.

There is a lot of consistent epidemiological data which indicate a higher incidence of lithiasis in western countries, mostly among males, the investigations showing the frequent association of hypercalciuria, one of the possible sources being the high bone resorption. It is obviously important, mostly to young patients, to understand the mechanism which produces the relapse of the stone episode in order to prevent it more efficiently.

So, we have enrolled in a comparative study 30 young patients, ages between 24 and 50 years, with recurrent kidney stones, group which was compared with a control group of healthy persons, perfect matched according to the age, BMI.

Exclusion criteria were: congenital malformations of the kidneys and ureter or bone system, hyperparathyroidism, renal tubular acidosis, inflammatory bowel syndrome, treatment with biphosphonates, hypogonadism, Cushing syndrome, long treatment with thiazidic
diuretics, calcium or Vitamin D, obesity (BMI > 30 k/m2).

Both groups were investigated on calcemia, phosphate, PTH, Vitamin D3, alkaline phosphates and osteocalcin. Calcium and phosphate in 24 hour urine were also measured and bone mineralization with DXA both on lumbar and coxo-femoral region.

The RN and CTR groups did not display any differences regarding the subject’s age, weight, height or BMI (Table 1.). Calciuria was significantly higher in the RN group (p<0.001, Fig. 1.). Although in the normal range, serum Ca was slightly higher, it was also significant in the RN group (p<0.05, Fig. 1.). No differences in serum and urinary phosphate were observed between the two groups (Fig. 1.). An important number of volunteers from both groups had 25OH-D3 levels in the vitamin D insufficiency (25OH-D3 between 20 and 30 ng/mL) or deficiency (25OH-D3 < 20 ng/mL) range. Patients with RN had significantly lower 25OH-D3 levels than healthy volunteers (p<0.01). Mean PTH and AP levels from patients with RN were within the normal range, although higher than the levels found in the CTR group (p<0.01). Serum PTH and 25OH-D3 were inversely correlated in both RN and CTR groups (p<0.001, data not shown). We found no differences between the two groups regarding osteocalcin. BMD, T and Z scores from patients with RN were significantly lower both at the lumbar (p<0.01) and total hip (p<0.05) regions (Fig. 1.). BMD was inversely correlated with PTH and AP levels (p<0.001) and directly correlated with 25OH-D3 levels (p<0.01) in the RN, but not in the CTR group (Table 1.). Urinary calcium excretion was strongly correlated with BMD in the RN group (p<0.001) and showed weak correlation with lumbar (p<0.05), but not hip BMD in the CTR group (Table 1, Fig. 2.).

Table 1. Mean age, height, weight and BMI of the control and relapsing lithiasis groups, expressed as mean SD. No significant differences were present.

<table>
<thead>
<tr>
<th>Group name</th>
<th>Control</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Age (years)</td>
<td>35.6 ± 6.9</td>
<td>37.2 ± 7.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78.8 ± 7.5</td>
<td>77.5 ± 8.8</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.75 ± 0.05</td>
<td>1.76 ± 0.06</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.6 ± 2.4</td>
<td>25.1 ± 2.6</td>
</tr>
</tbody>
</table>
There are only a few genetic conditions augmenting the risk of RN. However, the number of patients with nephrolithiasis has been increasing constantly around the world, especially in the advanced countries. The changes in the environmental factors seem to be very important, but they are still incompletely defined. IH is one of the most important risk factors of calcium RN. Our RN group had higher urinary calcium excretion compared to CTR (p<0.001, Fig. 1.). The origins of hypercalciuria can be: increased bone resorption, increased calcium absorption from the gut and/or urinary loss. However, all three conditions may be present in the same patient. Several clinical studies suggest that RN and IH are associated with increased bone turnover and reduced BMD, making plausible the hypothesis of high turnover bone resorption as the origin of RN in many cases. Our RN group had significantly higher serum AP levels (p<0.01, Fig. 2.), a parameter that might indeed reflect increased bone turnover. Serum osteocalcin, repeatedly found by only one group as increased in patients with RN, was not significantly modified in our study (Fig. 2.). All densitometry parameters were significantly decreased in the RN group vs. CTR (Fig. 3.). AP and calciuria were inversely correlated to BMD, incriminating higher bone turnover as an origin of both bone demineralization and increased urinary Ca excretion (Table 2, Fig. 3.). Interestingly, calciuria was mildly correlated to lumbar BMD also in the CTR group (p<0.05, Fig. 3.). Hypercalciuria is indeed proposed as a mirror of higher bone turnover and a risk factor for low bone mass in the general population.

**Fig. 1.** Serum (upper panel) and urinary (lower panel) calcium (left) and phosphate (right) in the control (black bars) and relapsing lithiasis (white bars) groups. Results are shown as mean ± SD. * p<0.05; ** p<0.001

**Fig. 2.** Serum 25OH-D3 (up, left) PHT (up, right) alkaline phosphate (down, left) and osteocalcin (down, right) in the control (black bars) and relapsing lithiasis (white bars) groups. Results are shown as mean ± SD. ** p<0.01
Table 2. The correlation coefficient between BMD in the lumbar (second column), femoral (third column) regions and PTH, 25OH-D3, calciuri, alkaline phosphatase levels in the control (upper panel) and relapsing lithiasis (lower panel) group

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Lumbar BMD</th>
<th>Femur BMD</th>
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<tr>
<td></td>
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<tr>
<td>PTH</td>
<td></td>
<td>-0.058</td>
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<tr>
<td>25OH-D₃</td>
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<td>0.191</td>
<td>0.010</td>
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<tr>
<td>Calciuria</td>
<td></td>
<td>-0.321 *</td>
<td>-0.240</td>
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<tr>
<td>Alkaline phosphatase</td>
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<td>-0.114</td>
<td>-0.273</td>
</tr>
</tbody>
</table>

<table>
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<tr>
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<th>Relapsing lithiasis</th>
<th>Lumbar BMD</th>
<th>Femur BMD</th>
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<tr>
<td>PTH</td>
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<td>-0.631 ***</td>
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<td>0.549 **</td>
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<td>-0.687 ***</td>
<td>-0.716 ***</td>
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<tr>
<td>Alkaline phosphatase</td>
<td></td>
<td>-0.688 ***</td>
<td>-0.645 ***</td>
</tr>
</tbody>
</table>

**Fig. 3.** Bone mineral density (BMD, upper panel), T score (middle panel) and Z score (lower panel) at the lumbar spine (L1-L4, left) and femoral (right) level in the control (black bars) and relapsing lithiasis (white bars) groups. Results are shown as mean ± SD. * p<0.05 **
An important question is to define the mechanisms underlying the modifications of Ca and bone metabolism in patients with RN. Higher PTH levels and/or sensitivity to PTH might link high bone turnover to increased risk of RN and bone loss. Different investigators found increased, unchanged or even decreased levels of PTH in patients with RN.

Older, but also younger people frequently have low vitamin D levels, possibly correlated to lower sunlight exposure. Moreover, patients having various pathological states, such as cardiovascular or autoimmune diseases, as well as patients at risk for osteoporosis have low vitamin D levels. Although vitamin D depletion could merely be a marker of frailty and generally does not reflect tissue sensitivity to its actions, vitamin D supplementation is certainly beneficial for bone mass acquisition and prevention of osteoporosis. The levels of 25OH-D3 were in the range of hypovitaminosis in many patients from both the RN and CTR groups. Mean 25OH-D3 of RN volunteers was, however, significantly lower (P < 0.01). Moreover, 25OH-D3 levels were inversely correlated with PTH and directly correlated with lumbar and hip BMD in the RN group. Vitamin D hypovitaminosis may cause a rise in PTH through lack of negative feedback, thereby being indirectly involved in the increase of bone turnover. Vitamin D deficiency may well be another environmental modification caused by modern life and favoring RN. Consequently, vitamin D repletion might be beneficial in RN through reversal of PTH levels and decrease of bone resorption and hypercalciuria. Antiresorptive therapy, such as bisphosphonates, may be a logical therapeutic solution to prevent bone loss and also decrease calciuria and RN risk, as proposed by other authors.
II.1.3 LOCAL ANALGESIA DURING ESWL

Urologic surgery means:
1. Endoscopic procedures performed for diagnosis (urethroscopy, cystoscopy) or therapy (transurethral resection of the prostate, transurethral resection of bladder tumour, elimination of calculi in the urinary tract);
2. Surgeries performed by percutaneous path (punctures, drainages, removal of calculi);
3. Conventional, open surgeries (bladder, prostate and kidneys);
4. Robotic surgery.

More and more patients referring to the urologist are elderly, a group characterized by numerous physiological alterations and comorbidities. Since the elderly may present numerous coexisting affections, a tremendous importance is granted to the pre-anaesthetic medical examination.

THE PRE-ANESTHETIC MEDICAL EXAMINATION

It has the following goals:
- anamnesis and careful clinical examination;
- evaluation of specialty tests, explorations and consult;
- informing the patient about the anesthesia, pre-surgery management, pain treatment - this stage of informing is necessary, as the understanding of the procedures reduces anxiety and the post-surgery cooperation becomes easier;
- to obtain the written consent of the patient or the family.

The old patient is sometimes dehydrated, poorly fed. After further talks with the patient, or his relatives, the medical history is thoroughly known: previous surgeries, current functional status, full index of the drug treatment administered at home (eventual drug interactions are thoroughly monitored). The careful clinical examination makes it possible to integrate the patient within a group of anesthetic risk (ASA score), and also to establish the degree of difficulty for general or spinal anesthesia. Evaluation through laboratory tests is compulsory, permitting correction in pre-surgery phase of the eventual dysfunctions (blood transfusions, electrolytic corrections, etc).

The anesthesiologist prescribes:
- anxiolytic medication (DIAZEPAM 1tb every 12 hours – in the evening and in the morning of surgery);
- the sampling of some analyses necessary on the day of the surgery (glycemia, ionograms, coagulation);
- administration of antibiotic prophylaxis for patients with risk of endocarditis.

Prophylactic pre-surgery antibiotic therapy is applied depending on the type of surgery, on the risk of appearance or extension of a series of inflammatory processes (according to protocols specific to each clinic in part). They then explain to the patient the way in which he will follow his treatment in the hours prior to the surgery: the administration of oral antidiabetics and insulin is interrupted, starting with the evening of surgery. The administration of the cardiac treatment is continued (antiarrythmics, Beta blockers, antihypertensives, etc.), as well as the administration of the treatment for thyroidal and psychiatric affections; in the case of patients pursuing treatment with oral anticoagulants, oral administration is interrupted and injectable forms are administered, according to a series
of protocols, taking into consideration the values of the coagulation tests.

The patient is advised not to consume solid foods starting with 10-12 hours prior to the surgery and liquids 4-6 hours.

Urologic surgeries may be performed by using the following anesthetic techniques:

**LOCAL ANESTHESIA:** may be useful in short-term diagnostic explorations. It uses Xylocaine gel 2%, introduced at urethral level. The endoscopic examination may be performed after 3-5 min (time necessary for the installation of the anesthetic effect). In the case of male patients, local anesthesia is supplemented by the use of intravenously administered analgesics (Ketorolac, Tramal, etc.).

**SPINAL ANESTHESIA:** is a technique of regional anesthesia, involving the administration of an anesthetic substance in the subarachnoid space. Given the fact that spinal anesthesia is invasive, there is a constant need to impose rigorous measures for limiting the contamination in the puncture region, and implicitly of the nervous structures. As a result, the person performing the technique, exactly like surgeons, should take all measures to prevent and limit contamination. Using the mask and cap, as well as sterile water and surgical soap for the decontamination of the hands, are compulsory. At the same time, the anesthetist, as the surgeon, must wear a surgical coat and gloves.

The technique involves the advance of a special needle, introduced between 2 vertebral bodies, up to the subarachnoid region. The correct position in the subarachnoid space is proven when LCR is highlighted – “clear, like rock water”, colourless. After highlighting the liquid, the syringe containing anaesthetic is firmly attached and the injection of the anaesthetic continues, in a slow rhythm, 1ml in 5-10 seconds. At the end of the injection, the puncture needle is withdrawn, and the region is covered with sterile dressing.

In its path to the subarachnoid space, the needle crosses the following structures: skin, subcutaneous cell tissue, supraspinous ligament, dura mater, subarachnoid region.

Normal functions are lost in the following order:

- Sympathetic function;
- Superficial tactile sensitivity and thermal sensitivity- the patient perceives heat in the inferior part of the body, under the level of the spinal anaesthesia;
- Superficial painful sensitivity - absence of pain upon pricking;
- Profound painful sensitivity (visceral pain disappears) this is the moment to begin the surgery;
- Motorparalysis - the patient cannot move his lower limbs, even if he wants to;
- Proprioceptive sensitivity disappears in 10 minutes.

Advantages of spinal anaesthesia:

- short period from administering to onset;
- very good analgesia and muscular relaxation;
- the patient is conscious, he can cooperate with the physician, indicate the eventual events that occurred during the anaesthesia and surgery;
- the patient does not need the prosthesis of the upper breathing paths, he breathes spontaneously;
- quicker recovery after the anaesthesia;
- the patient does not need sophisticated monitoring;
- minimizes the reaction to surgical stress;
• reduces the intra-surgery blood losse, compared with general anaesthesia;
• reduces the risk of trombo-embolism in the post-surgery period;
• reduces the patients morbidity and mortality with a high risk in this respect.

Disadvantages of spinal anaesthesia: temporal limitation of the block – in surgeries extending over longer periods of time, the effect may disappear, extra measures of analgesia and sedation being necessary.

Indications for spinal anaesthesia: lower abdominal surgery; surgery of the lumbar, perineal, gluteal region; surgery of the lower limb; it could represent an election technique for the patient with increased anaesthetic risk.

Contraindications of spinal anaesthesia:

a. Absolute contraindications:
   - patient’s refusal;
   - coagulation disorders;
   - thrombocytopenia;
   - shock, regardless of its etiology;
   - sepsis;
   - infection of the puncture region;
   - increased intracranial pressure.

b. Relative contraindications:
   - non-cooperative patient;
   - pre-existing neurological diseases;
   - severe stenose of the aorta and of the mitral valves.

Complications of spinal anaesthesia: toxic reactions; arterial hypotension; anaphylactic reactions; acute urine retention; neurological complications: transitory neurological symptoms, reduction of hearing, back pain, equilibrium disorders, paralysis of the cranial nerves, neurological injuries, total spinal anaesthesia, meningitis, subdural hematoma, and headache.

The preoccupation to offer our patients with kidney stones a better comfort during the Extracorporeal Shock Wave Lithotripsy (ESWL) sessions has been debated in the article: THE EFFICACY OF PIROXICAM/LIDOCAINE/CYCLOBENZAPRINE HYDROCHLORIDE TOPICAL GEL IN THE PAIN MANAGEMENT DURING EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY (ESWL), published in Farmacia, in 2016.

The principle of ESWL is based on stone disintegration with the help of acoustic waves (so called shock waves) which are produced outside the body by special devices that are focused on the target shown with ultrasound or X-Ray system. These shock waves pass through the skin and all tissues in their path and discharge the energy on the surface of the stone. More or less the procedure is painful and this is the reason why, since the year of its introduction in daily practice, many strategies have been discussed to prevent patient suffering.

It is clear that for patient comfort and lowering the costs of the procedure it is better to avoid laborious and risky techniques. We must keep in mind that the pain is perceived by different patients in different ways upon personal sensibility, the number of shocks and their intensity and we must use the analgesic upon his requirements.

We have investigated a combination of anti-inflammatory drugs with a topical
anesthetic for the first time in the case of the patients before ESWL.

The inclusion criteria were adult patients with renal or urethral stones, unilaterally or bilaterally localized, with the diameter smaller than 20 mm, eligible for ESWL, without known hypersensitivity to piroxicam, cyclobenzaprine, lidocaine or any other ingredient of the product and no previous exposure of ESWL. Exclusion criteria for this study were: stones larger than 20 mm, known hypersensitivity to any of the ingredients, asthma, nasal polyposis angioedema or rash induced by acetylsalicylic acid or other non-steroidal drug, pregnancy, bleeding disorders, active urinary tract infection, age under 18 years. The patients were advised to stop using anticoagulant products 10 days prior, and any NSAIDs treatment 2 days before the ESWL procedure. Prior to the ESWL procedure, the data recorded for each of the patient included age, gender, weight, height, the size and stone localization. Enrolled individuals were thoroughly evaluated through: clinical examination, family history, baseline biological and hematological tests, urine microscopy with culture and sensitivity. An intravenous urography (IVU) was done in all the cases to assess the anatomical and functional aspects of the urinary system along with stone characteristics like size and position.

A second-generation electro hydraulic lithotripter with unique radiologic guidance was used. The equipment outputs 1 shock/second. Usually the treatment consists of up to 4000 shocks for ureteral stones and 3000 shocks for renal stones in sessions of 300 shocks. Initially low intensity shocks were applied (17.5 kV), which gradually increase (up to 19 kV). The patients were randomly assigned to one of the 3 groups: group A (topical analgesia with the gel containing piroxicam 0.5%, lidocaine 2%, cyclobenzaprine hydrochloride 0.5%, 30 minutes prior to ESWL), group B (topical analgesia with the same gel, 60 minutes prior to ESWL) and group C (no treatment prior the ESWL). For the patients in group A and B, 1g of gel was spread and rubbed gently into the skin at the site of ESWL application, till complete absorption. Each patient scored the pain before the procedure using a VAS (Visual Analogue Scale 0 – 10, 0 meaning no pain and 10 excruciating pain). Each individual was placed with an intravenous catheter before the procedure in order to be easily approached in case of analgesia requirement. If necessary, the patient received rescue medication – 100 mg of tramadol. After the ESWL, each subject was asked to score the pain perceived during the procedure. Additionally, the rescue medication, number and intensity of shocks and procedure duration were quantified for each of them.

The VAS score for the pain perceived before and during the ESWL, the level of tramadol consumption are represented in Table 1. Mean VAS score during ESWL in group A was 3.76 ± 1.03, in group B 3.40 ± 0.83 and in group C 5.38 ± 1.46. The VAS score in group A and group B was significantly lower than in group C (control): Z-test + 6.20, p < 0.0001, Z-test + 8.59, p < 0.0001, respectively.
Table 1. Data for pain VAS score, rescue medication, adverse reactions

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS score before ESWL</td>
<td>0.43 ± 1.04</td>
<td>0.53 ± 0.83</td>
<td>0.60 ± 0.93</td>
<td>0.49</td>
</tr>
<tr>
<td>VAS score during ESWL</td>
<td>3.76 ± 1.03</td>
<td>3.40 ± 0.83</td>
<td>5.38 ± 1.46</td>
<td></td>
</tr>
<tr>
<td>(p value*)</td>
<td>p&lt;0.0001*</td>
<td>p&lt;0.0001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference between VAS</td>
<td>3.32 ± 1.47</td>
<td>2.87 ± 1.24</td>
<td>4.78 ± 1.59</td>
<td></td>
</tr>
<tr>
<td>score during and before</td>
<td>p&lt;0.0001*</td>
<td>p&lt;0.0001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESWL (p value*)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rescue medication</td>
<td>7 (7.78%)</td>
<td>4 (4.70%)</td>
<td>11 (13.58%)</td>
<td></td>
</tr>
<tr>
<td>ODD Ratio**</td>
<td>0.57</td>
<td>0.34</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p value for the statistical significance between active and control group  
** relative risk for appealing at rescue medication in group A and B versus group C

Topical application of a gel with the combination piroxicam/lidocaine/cyclobenzaprine hydrochloride before the ESWL was linked with significantly lower value of VAS score for the pain during ESWL. These results suggested that topical analgesic treatment before ESWL provides significant relief for the pain during ESWL in comparison with no treatment. A statistically significant difference was noticed also between groups A and B: Z-test = 2.20, p<0.05. Although both of the therapy plans, 30 or 60 minutes before lithotripsy, were effective in pain alleviation, the use of the gel 60 minutes before the procedure was significantly more efficient. The topical analgesic gel before lithotripsy also reduced the usage of rescue medication. If in group C 11 patients (13.58%) asked for medication, in group A and B only 7 (7.78%), respectively 4 (4.7%) subjects required rescue medication. A significantly lower risk for the need of rescue medication was observed in group A and B in comparison with group C – OR = 0.54 and 0.34, respectively. By assessing all data, only 11 men (10.02%) and 11 women (7.43%) asked for rescue medication. No side effect and local skin reaction were reported in the groups that received topical medication. The Pearson correlation coefficient for body mass index (BMI), size stone, number of shocks and VAS score during lithotripsy was calculated (Table 2.). No significant correlation between BMI, size stone and number of shocks to VAS score was detected in groups B and C. A significant correlation between BMI and stone size with VAS was highlighted for the patients in group A.
Table 6. Correlation matrix in group A, B and C

<table>
<thead>
<tr>
<th>Correlation in group A</th>
<th>Pearson correlation</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age and VAS score</td>
<td>-0.17</td>
<td>0.10</td>
</tr>
<tr>
<td>BMI and VAS score</td>
<td>-0.14</td>
<td>0.19</td>
</tr>
<tr>
<td>Stones size and VAS score</td>
<td>0.05</td>
<td>0.65</td>
</tr>
<tr>
<td>Number of shocks and VAS score</td>
<td>0.14</td>
<td>0.21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Correlation in group B</th>
<th>Pearson correlation</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age and VAS score</td>
<td>-0.09</td>
<td>0.40</td>
</tr>
<tr>
<td>BMI and VAS score</td>
<td>-0.21</td>
<td>0.06</td>
</tr>
<tr>
<td>Stones size and VAS score</td>
<td>0.01</td>
<td>0.95</td>
</tr>
<tr>
<td>Number of shocks and VAS score</td>
<td>0.12</td>
<td>0.26</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Correlation in group C</th>
<th>Pearson correlation</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age and VAS score</td>
<td>-0.11</td>
<td>0.35</td>
</tr>
<tr>
<td>BMI and VAS score</td>
<td>-0.17</td>
<td>0.13</td>
</tr>
<tr>
<td>Stones size and VAS score</td>
<td>0.02</td>
<td>0.89</td>
</tr>
<tr>
<td>Number of shocks and VAS score</td>
<td>-0.05</td>
<td>0.65</td>
</tr>
</tbody>
</table>

ESWL represents the first treatment option of renal stone between 5 and 20 mm, applied in 90% of cases [24]. With the first generation of lithotripters that were developed in the 80’s, the procedure was performed under general or spinal anesthesia, because of the extreme pain [25]. The technique evolved and nowadays, optimized devices, with new types of shock wave generators, improved ESWL procedure making it better tolerated and so that it can be performed under analgesia, rather than anesthesia [26]. Although the procedure remains painful, in most of the cases the patient tolerates the pain without the use of any analgesic intervention. In current practice, the patients receive no analgesic treatment before intervention, but have the possibility to ask for rescue medication (parenteral opioids) in case of unbearable pain during ESWL.

The opioids have the disadvantage of presenting a large number of side effects like respiratory depression, nausea and vomiting [27, 28]. Among the opioids, tramadol hydrochloride is one of the most used analgesics in rescue medication for ESWL [26, 27]. In usual therapeutic doses, no clinically significant respiratory depression occurs [26, 29], however, parenteral doses 100 mg of tramadol used during ESWL are linked with high rates of nausea and vomiting - 25% [26, 30, 31]. Therefore, further clinical and experimental trials are required to investigate the possibilities of limiting even more the use of analgesics like tramadol. Topical anaesthetic application (especially lidocaine/ prilocaine) before the procedure was also reported in different studies [32-34]. It was used alone or in combination with analgesics (NSAIDs or opioids) and it was found to be safe and effective in some of the studies [32-34].

Kumar et al. determined in a study of 240 patients undergoing ESWL that the use of a topical anesthetic: EMLA (lidocaine 2.5%, prilocaine 2.5%) before the procedure, together with orally administered diclofenac, prevented the need of parenteral analgesics [35]. Basar included in a trial 160 patients undergoing ESWL and determined that local EMLA led to a decrease of intravenous analgesic (fentanyl), confirming the results of a previous research, performed by Xavier [36]. NSAIDs agents (e.g.: diclofenac, ketorolac and piroxicam) can also be used for pain relief during the ESWL procedure [26].
Previously, they were used intravenously, intramuscularly, orally or rectally, but studies for the effect of topical NSAIDs were also performed, with good results. Iqbal, in a study performed on 50 patients, determined that diclofenac is safe for analgesia during ESWL, and diclofenac gel together with diclofenac intramuscular administration presented a better pain relief control compared to diclofenac gel alone [37].

Moazeni-Bistgani et al. emphasized in a study on 159 patients diagnosed with urolithiasis undergoing ESWL, that both lidocaine gel and piroxicam gel administered 30 minutes before the procedure, efficiently improved pain perception by the patients and the necessity of intravenous analgesia [38]. Considering these findings, cutaneous diclofenac and piroxicam seem to find their place in the treatment plan for the patients undergoing ESWL. The present research was focused on investigating the possibility to increase the comfort of the patients undergoing ESWL, by mitigating the pain and, as well, reducing the use of rescue medication, when applying a cutaneous gel containing the combination of an NSAID, a topical anaesthetic and a tricyclic analgesic before the procedure. From our knowledge, this is the first study focused on the effects of a topical product containing a combination of NSAID, local anaesthetic and tricyclic painkiller used in the pain management during ESWL. The results are in accordance with previous researches which concluded that topical anaesthetic and topical NSAIDs represent a useful option for pain management during ESWL. In addition, the current study determined that the timing for topical application is very important, as superior results were obtained in the case of 60 minutes compared to 30 minutes administration before ESWL. The timing of topical agent application is essential for both pain reduction and rescue medication consumption. The patients in the group that received the gel 60 minutes before the procedure presented lower pain score and seldom asked for rescue medication. It seems that the 60 minutes application prior to the procedure provides a more close to maximum effect of this gel. As with many other studies on topical agents, especially topical NSAIDs [26, 37], we consider that further research is necessary to investigate the best moment for topical analgesics administration.

The use of the combination piroxicam 0.5%, lidocaine 2% and cyclobenzaprine hydrochloride 0.5% in a single cutaneous application offers a better compliance of the patient to the treatment than the standard protocol, which does not use any analgesic medication before the ESWL procedure. Although the use of the gel 30 minutes before the procedure was found effective, the 60 minutes application before the procedure significantly reduced the pain perception and the level of opioid consumption.
II.1.2. X-RAY EXPOSURE IN ESWL VERSUS RETROGRADE URETEROSCOPY

During modern procedures to treat the ureteric stones we need to use X-Ray in order to focalize the stone and to see the possible residual fragments. The impact of the exposure was the main goal of another study: EXTRACORPOREAL SHOCK WAVES LITHOTRIPSY VERSUS RETROGRADE URETEROSCOPY: IS RADIATION EXPOSURE A CRITERION WHEN WE CHOOSE WHICH MODERN TREATMENT TO APPLY FOR URETERIC STONES? Published in the Bosnian Journal of Basic Medicine and Science. 2014; 14 (4): 1-5. © 2014, ABMSFBIH.

We are familiar that any of the procedures mentioned above has its own advantages and disadvantages, and sometimes we do not know what the best option is in order to be more successful.

ESWL has the advantage of a very short stay into the hospital (just for a few hours!), can be performed with sedoanalgesia, but we cannot predict when the fragments will be eliminated, when this outcome will occur.

On the other hand, retrograde ureteroscopy is more aggressive, has potential risk of infection, but the stones are fragmented under direct view, and all this in a longer hospitalization.

We have analyzed the 2 procedures from another point of view, the irradiation of the patient during the intervention and we have noticed interesting results.

From the total of 175 patients, in 92 of them we performed ESWL and the rest of 83 patients underwent URS. In terms of gender distribution this study is comprised of 105 men and 70 women; sex ratio M/F = 1.5. The patient age was ranged between 19 and 81 years, with a mean of 49.62 years (SD = 15.61 years, 95% CI) and no significant difference between genders (p=0.864). One hundred and seven patients had BMI > 25kg/m2 (65 men and 42 women) and 68 patients had BMI < 25kg/m2 (40 men and 28 women). No significant differences of BMI mean were observed between the URS and ESWL groups. There were no significant statistical differences in terms of BMI between men and women (p=0.847, SD  = 4.8). One hundred twenty-eight patients had abdominal obesity and 47 patients had normal waist circumference. Depending on the location of the calculi, 90 patients (51.4%) presented with lumbar ureteral stones (52 men and 38 women) and 85 patients (48.6%) pelvic ureteral stones (53 men and 32 women). The mean stone size was 6 (3-11) mm in the ESWL group and 7.1 (4-13) mm in the URS group; with no significant statistical difference (p>0.05) between these two groups.

Patient radiation dose was expressed in terms of total PKA in cGy cm2. Patients who underwent ESWL for lumbar ureteral lithiasis were exposed to an ionizing radiation dose between 154 cGy cm2 and 890 cGy cm2, with a mean of 509 cGy cm2 (SD = 180 cGy cm2), while for those who were treated for pelvic ureteral lithiasis, the received dose was between 111 cGy cm2 and 910 cGy cm2, with a mean of 342 cGy cm2 (SD = 201 cGy cm2). In the URS group for lumbar ureteral lithiasis the radiation dose was between 200 cGy cm2 and 2304 cGy cm2, with a mean of 892 cGy cm2 (SD = 436 cGy cm2), while patients with pelvic ureteral lithiasis received a dose between 166 cGy cm2 and 1765 cGy cm2, with a mean of 601 cGy cm2 (SD = 429 cGy cm2). Patients with BMI < 25 kg/m² subjected to ESWL
received a dose between 122 cGy cm$^2$ and 890 cGy cm$^2$, with a mean of 316 cGy cm$^2$ (SD = 177 cGy cm$^2$) and those subjected to URS received a dose between 166 cGy cm$^2$ and 1207 cGy cm$^2$, with a mean of 416 cGy cm$^2$ (SD = 289 cGy cm$^2$).

In terms of average radiation dose the study groups presented the following differences. In patients suffering from pelvic ureteral stones, especially those with lumbar ones, the average radiation dose was higher in the URS group (p=0.001). In obese patients the average dose of radiation was higher in URS group (p=0.001), while in patients with normal weight the average radiation only tended to be increased in the URS group (p=0.089).

By comparing the groups in terms of BMI and waist circumference (Table 1) it is evident that all the groups with obese and abdominally obese patients received radiation doses higher than the normal weight group.

**Table 7. Influence of body mass index and waist circumference upon patient radiation**

<table>
<thead>
<tr>
<th>Ureteral stone group</th>
<th>Air kerma-area product (cGy cm$^2$)</th>
<th>$p$</th>
<th>Air kerma-area product (cGy cm$^2$)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BMI$&gt;$25</td>
<td>BMI$&lt;$25</td>
<td>Abd. obesity</td>
<td>Normal waist circ.</td>
</tr>
<tr>
<td>Lumbar</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESWL</td>
<td>567</td>
<td>386</td>
<td>555</td>
<td>392</td>
</tr>
<tr>
<td>URS</td>
<td>1089</td>
<td>544</td>
<td>1004</td>
<td>558</td>
</tr>
<tr>
<td>Pelvic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESWL</td>
<td>420</td>
<td>246</td>
<td>426</td>
<td>213</td>
</tr>
<tr>
<td>URS</td>
<td>815</td>
<td>338</td>
<td>663</td>
<td>303</td>
</tr>
</tbody>
</table>

In terms of average exposure time depending on location of the ureteral stone, the studied groups presented the following differences (Table 8):

**Table 8. Influence of body mass index and waist circumference upon exposure time**

<table>
<thead>
<tr>
<th>Ureteral stone group</th>
<th>Procedures</th>
<th>Exposure time (s)</th>
<th>$p$</th>
<th>Exposure time (s)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BMI$&gt;$25</td>
<td>BMI$&lt;$25</td>
<td>Abd. obesity</td>
<td>Normal circum.</td>
</tr>
<tr>
<td>Lumbar</td>
<td>ESWL</td>
<td>209</td>
<td>160</td>
<td>0.001</td>
<td>208</td>
</tr>
<tr>
<td></td>
<td>URSR</td>
<td>286</td>
<td>153</td>
<td>0.016</td>
<td>268</td>
</tr>
<tr>
<td></td>
<td>$p$</td>
<td>0.014</td>
<td>0.647</td>
<td>-</td>
<td>0.036</td>
</tr>
<tr>
<td>Pelvic</td>
<td>ESWL</td>
<td>207</td>
<td>185</td>
<td>0.567</td>
<td>209</td>
</tr>
<tr>
<td></td>
<td>URSR</td>
<td>241</td>
<td>125</td>
<td>0.002</td>
<td>207</td>
</tr>
<tr>
<td></td>
<td>$p$</td>
<td>0.414</td>
<td>0.061</td>
<td>-</td>
<td>0.943</td>
</tr>
</tbody>
</table>
In obese patients with lumbar ureteral stones, the average exposure was increased in the URS group (p=0.014) versus the ESWL group, with a similar observation in patients with abdominal obesity (p=0.036).

The average exposure shows no differences between the URS and ESWL groups in patients with pelvic ureteral stones and with obesity or abdominal obesity.

In most studies success rate is, as expected, the main criterion for comparison between the two procedures. Many authors who compared the stone-free rate for ESWL versus URS revealed the superiority of the last one. In 156 patients, of which 87 underwent URS and 69 ESWL, Hendrikx revealed a stone-free rate of 51% for ESWL compared to 91% for URS [39]. In a meta-analysis from 2012, Aboumarzouk revealed a stone-free rate lower for ESWL (7 trials; 1.205 participants), compared to URS (5 studies, 751 participants), but with a lower rate of complications [40]. According to EAU guidelines, the stone-free rate in the case of pelvic ureteral stones is ~ 82%, similar for ESWL and URS. In case of lumbar ureteral stones, the stone-free rate of 93% is in favor of URS compared to 74% for ESWL.

Therefore, urologists choose URS as a first line treatment for ureteral lithiasis. This option is confirmed by a study from Canada, Orduna et al. showing that ESWL decreased from 68.5% in 1991 to 33.7% in 2010, while URS increased from 24.6% to 59.5% (URS almost replaced ESWL) [41].

The side effects of exposure to ionizing radiation are well known, with erythema being the first visible complication. In the case of single-delivery radiation the risk threshold is 20,000 - 50,000 cGy cm² for simple transient erythema and > 150,000 cGy cm² for transient erythema with edema and acute ulceration. The radiation doses for our patients treated by ESWL or URS were lower than the mentioned threshold for simple erythema and we emphasize that the results presented here are doses delivered along the entire surgical procedure. The increasing use of X-rays for the management of urinary lithiasis (diagnosis and treatment) could raise the question of radiation exposure of patients and urologists. The dose of radiation per patient has increased 6 times in the United States since 1980 and because of this there have been concerns regarding the increasing incidence of ionizing radiation-induced cancers.

The radiation dose received by the patient varies depending on many factors: size of the stones, operator experience, radio-opacity of the stones, patient’s abdominal obesity, stone enclavation in the ureteric mucosa, intraoperative difficulties due to anatomical variation, etc. In addition, the patient is subjected to X-ray ionizing radiation in order to establish the diagnosis and for post-therapeutic control. Thus, a patient with ureteric stones during iv urography receives an average radiation dose of 2.5 cGy cm² (depending on the number of X-ray pictures made), and during the post-procedures they further receive an average of 0.7 cGy cm², depending on the number of radiographs necessary. Patients undergoing ESWL may receive a radiation dose between 2.33 cGy cm² and 398 cGy cm², while for URS the dose is between 2.23 cGy cm² and 590 cGy cm². This varies depending on the patient’s weight and on the stone size. Obese patients can receive 3 times higher doses. The urologist’s knowledge regarding ionizing radiation is another important aspect, because urologists with more than 2 years of experience, who monitor the radiation dose during surgery, can decrease it by up to 55%. Probably this is not the same for the urologists with less experience. The average
radiogenic risk for genetic defect associated to treatments of proximal and distal ureteral stones was found to be 2.5 and 24.4 per million of births, respectively. The radiation risk from a typical fluoroscopy guided ESWL treatment of ureteral stones is low. Although the measured doses were infinitesimal, ESWL cannot be considered a safe procedure, because of the cumulative effect due to the repetition of procedures in addition to pre and post-examination exposures.

Comparative evaluation of the level of ionizing radiation using air kerma-area product for a patient with the same lithiasis pathology (including stone location and size) treated with different therapeutic methods revealed higher values of air kerma-area product in patients subjected to URS versus ESWL, also confirmed by other studies. Patients with BMI > 25kg/m² received higher radiation doses than those with BMI < 25kg/m². However, all these ionizing radiation levels are low, so we consider that urologists must have these issues in mind when treating patients with recurrent urolithiasis, possibly requiring repeated X-ray guided endourological procedures. On the other hand, further research on the relation between re-treatment rate and radiation exposure, until the stone free status is reached, appear to be of particular interest.
II.1.5. EXPULSION THERAPY FOR SMALL URETERIC STONES

The project: **EVALUATION OF THE BENEFITS OF POTASSIUM AND MAGNESIUM CITRATE TRIBASIC VERSUS TAMSULOSIN IN PATIENTS WITH RENAL AND URETERAL STONES, OR WITH RESIDUAL FRAGMENTS (LESS THAN 7mm) AFTER EXTRACORPOREAL SHOCK WAVES LITHOTRIPSY, RETROGRADE URETEROSCOPY OR PERCUTANEOUS NEPHROLITHOTOMY** is a grant conducted by associate Prof. Dr. Catalin Pricop, research team member Dr. Dragos Puia; Financing Agreement no. 15442/15.07.2016; period: 01.08.2016 - 31.07.2017, at the University of Medicine and Pharmacy Iasi.

Nephrolithiasis is a major cause of morbidity, with an incidence of 5 - 15% according to the available statistics, and a recurrence rate greater than 50%. Men tend to be affected more frequently than women. All geographical, cultural, and racial groups demonstrate a remarkable similarity in the incidence.

Unfortunately, we do not have any precise information regarding the incidence of nephrolithiasis in Romania, some estimations from a few years ago indicating numbers consistent with our geographical position (one in 11-12 people risk to experience renal colic during his lifetime).

Regarding the nephrolithiasis in the region of Moldavia, the Urology Clinic in Iasi is the only one available for a population of 5 - 6 million. In the last years, there has been a significant increased prevalence of nephrolithiasis, especially in people under the age of 45, with a high risk of relapse. Only in 2015, the expenses related to the hospital admissions and therapies for these patients were over 342,000 euros, 23.6% of them requiring an endourological emergency intervention in the first 24 hours after admission due to the special clinical situation (subintrant renal colic, obstructing ureteral stone with secondary infection).

Therefore, we are dealing with a major health problem that along with the patient suffering, brings increasing costs for the health budget.

This problem has three important directions:

1) The prevention of lithiasis, by raising awareness of the causes and risk factors, throughout the community and the general practitioners;

2) Therapies for the diagnosed patients: expulsive treatment or minimally invasive procedures (extracorporeal shock wave lithotripsy, retrograde ureteroscopy, percutaneous nephrolithotomy or laparoscopy) in case of stones with inadequate sizes for spontaneous passage;

3) Secondary prevention of lithiasis for patients with high risk of relapse (young patients, with bilateral stones, a family history of lithiasis, metabolic disorders, frequent episodes, etc.), dietary measures and adequate, personalized treatment, based on the chemical composition of the urinary calculi obtained either from the spontaneous passage, or through endoscopic removal, but also on a complete biochemical and metabolic evaluation.

The proved existence of alpha-adrenoreceptors in the ureter encouraged the study of the theory that alpha-receptor blockage in the ureter promotes muscle relaxation and lowers the peristalsis.

Alpha-receptor blockers were studied extensively in relation to the expulsive therapy
for kidney stones, large groups of patients being evaluated before and after extracorporeal shock waves lithotripsy. A meta-analysis highlighted some potential benefits of the alpha-blockers in terms of expulsion rate, with no significant decrease in the frequency of renal colic onset, therefore no decrease in the need for analgesic medication.

Tamsulosin 0.4mg (the most studied example) has a beneficial influence on the expulsion rate, with most of the studies highlighting this fact. We might be tempted to think of this as a drug class-effect, but Pedro et al. have proven that the administration of Alfuzosin, while improving the clinical state of the patient and lowering the time needed for expulsion, does not influence the spontaneous stone passage. Comparing the effect of Nifedipine and Tamsulosin on the ureter in vitro, Nifedipine has an equal relaxing effect on the proximal and distal ureter, while Tamsulosin has a greater relaxing effect on the distal ureter.

On the other hand, for decades, the scientific community worldwide has agreed on the fact that citrate administration in patients with lithiasis is useful. A variety of citrate-based products exists worldwide (Uralyt-U, Lithoren, Bicitra, Oracit, Polycitra, Polycitra-LC, Polycitra K, Cytra-2, Urocit-K). In Romania, at the present moment, only two products are officially available: Uralyt-U and Lithoren. It is proven that the intake of alkaline products increases the urinary elimination of the citrate.

Potassium and magnesium citrate are metabolized to bicarbonate, increasing the excretion of free bicarbonate ions in the urine, thus effectively raising the urinary pH. In the right dose, the citrates do not cause systemic alkalosis. The raise of the urinary pH increases cystine and uric acid solubility, therefore promoting the dissolution and elimination of the uric acid stones.

Potassium citrate also inhibits the crystallization and the spontaneous nucleation of calcium oxalate and calcium phosphate in hypocitraturic nephrolithiasis.

The adequate liquid intake as part of the dietary measures adapted to the lithiasic type has been already widely spoken of. Nobody doubts today that the passage of any stone, no matter how small, cannot be accomplished without an abundant liquid intake. Most of the authors agree on the fact that one of the most important measures in the prevention of lithiasis, regardless of the cause, is adequate liquid intake. The general recommendation for the conservative management of renal lithiasis is an adequate intake in order to promote a daily diuresis with a minimum of 2 litres daily.

When talking about liquids, we must take into account not only regular water, but also tea with a proven diuretic effect. It has a high reputation among the patients, most preferring it to regular medication due to various reasons (starting with financial reasons, but also local traditions and beliefs). The most famous teas for patients with lithiasis are: cherry stalk tea, corn silk tea, diuretic tea with a mixture of various plants. The pleasant taste of these teas makes them more accepted by the patients in comparison to regular water. On the other side, the fact that tea involves the boiling of water suggests that the salts and the impurities from the water are being removed and the drink itself becomes healthier. As Margaret Pearle says, it is by far easier to change people’s religion than their dietary habits. In Romania, Moldavia, and especially in the rural areas, it is generally believed that the consumption of tea is the first and the most important step in stone-elimination.

Fresh home-made fruit juices are preferred by a lot of patients, and even recommended in nephrolithiasis. Lemon juice, although sour (taste that suggests acidity), has in fact an
alkaline effect, the citrate being, as we have mentioned before, really beneficial in the prevention of crystallisation. Not only this juice, but others as well, rich in potassium and low in sodium, provide a lot of vitamins and minerals. Diabetics should drink these in moderation, as fruit juices are high in sugar. We should mention the melon diet, considered by most of the patients with lithiasis to be very effective, due to the well-known diuretic effect.

Mineral water intake has proven to be extremely useful for small calculi elimination. It’s worth mentioning though, that not any mineral water is recommended, but only the oligomineral and hypotonic ones.

While reviewing the current literature on the expulsive therapy, we cannot ignore other attempts to find different solutions. Therefore, Rowatinex contains a terpene combination, defined by the producers to have diuretic, anti-inflammatory and analgesic effects. As clinical trials have proven, Rowatinex can ease the symptoms associated with the stone elimination process. It might be odd, but the phosphodiesterase type 5 inhibitors (PDE5 inhibitor), traditionally used in the treatment of erectile dysfunction, have been evaluated for their possible benefits related to the stone-elimination process. Recently, researchers showed that sildenafil citrate can improve the chances of successful passage of a 5 - 10 mm distal ureteral stone, compared to placebo.

Therefore, patients with nephrolithiasis have a variety of options in terms of medication that promotes stone passage. While each has different advantages and disadvantages, a consensus between urologist worldwide has yet to be reached.

The novelty of this study lies in the comparison, for the first time worldwide, between two therapeutic solutions often recommended to patients with small calculi. The two products compared can be found in pharmacies, and patients have access to them with a simple medical prescription from any doctor.

The motivation for this project lies in real aspects of the current medical practice. At the present moment, there hasn’t been carried out any well-documented, multicentric, randomized, placebo-controlled study to determine the best therapeutic option. The premises of our research are:

- At the present moment, there isn’t any optimal therapeutic option, universally accepted;
- The guidelines and recommendations accompanying these medications are not always followed in the current medical practice;
- A lot of patients are reluctant to take the prescribed medication, as they put their faith in the adequate liquid intake, seen as the best therapeutic option on the internet;
- There are no studies to indicate which patients (patient profile, stone position) would benefit most from the alpha-blockers, or from the calcium channel blockers.

These aspects, along with the difference between the therapeutic guidelines and the medical practice, lay the foundation for this reasearch. The study follows a sufficiently-long period, with monthly evaluation based on well-documented sets of questions, in order to indicate the best therapeutic option (selective alpha-blocker, potassium and magnesium citrate tribasic or adequate liquid intake) that can assure the fastest stone elimination, with minimal discomfort.

This original comparison between the tree groups (Tamsulosin, Lithoren and control group) can bring new answers, as clarifying as possible, regarding the best therapeutic option
that promotes urinary stone passage.

**General and specific objectives of the project:**

We plan to assess the outcome during a 3 month period from initial randomization. We have two main objectives, both equally important:

A. Elimination of the stone or the residual fragments resulted after the modern extracorporeal and endourological therapies (extracorporeal shock waves lithotripsy, retrograde ureteroscopy or percutaneous nephrolithotomy);

B. Pain management during the stone elimination: assessment of pain intensity, duration and also the need for painkillers or endourological therapies (insertion of a double J stent, retrograde ureteroscopy, endoscopic meatotomy for a calculus which is impacted in the ureteral meatus, or even extracorporeal shock wave lithotripsy for acute renal colic, targeting the obstructing ureteral stones).

Included patients were randomized into three groups:
1. Group A: Tamsulosin 0.4 mg, one tablet/day, at night, for three months, along with adequate fluid intake;
2. Group B: Lithoren, 1 sachet, twice a day, dissolved in 500 ml of water/tea, for three months, along with adequate liquid intake;
3. Group C (control group): diuretic tea, minimum 2 litres per day.

The patients will be monitored monthly (or whenever needed, in the case of worsening clinical symptoms they might require hospital admission and unplanned emergency surgery).

Apart from the two main objectives, we are interested in assessing other important aspects as well:
- adherence to the treatment, tolerance, drug related adverse events;
- compliance with dietary recommendations (adequate fluid intake, limited consumption of animal protein, salt, refined sugars and soft drinks, healthy diet that contains fruits and vegetables, as well as diluted citrus juices);
- the challenges of implementing the lifestyle changes (this will lay the groundwork for optimal adherence in advance).
II.1.6. THE BONE METABOLISM OF LITHIASIC PATIENTS

The grant: BONE MASS, BONE TURN-OVER AND THE BIPHOSPONATES THERAPY AT THE PATIENT WITH RELAPSING KIDNEY STONES AND IDIOPATIC HYPERCALCIURIA was discussed with the occasion of presenting the ISI Thompson articles published in the last 5 years. The results were published in Acta Endocrinologica in 2015.

This grant was organized by the University of Medicine and Pharmacy “Grigore T. Popa” Iasi and had a team composed of Prof. Dr. Dumitru Branisteau and associate Prof. Dr. Didona Ungureanu, between 01.01.2012 - 20.12.2012, contract Nr. 28216 from 16.12.2011.

A cross sectional study was performed, including a group of 30 young male patients with RN and a group of 30 healthy, age and BMI (body mass index) matched controls (CTR). We evaluated calcium and phosphate metabolism, bone remodeling markers alkaline phosphatase (AP) and osteocalcin in serum and 24-hour urine samples, lumbar and hip BMD.

We observed higher values of serum calcium (p<0.05) and 24 hour urinary calcium (p<0.001) in the RN group. Parathyroid hormone (PTH) and AP were also higher in the RN group (p<0.01), whereas serum 25OH-D3 was lower (p<0.01). BMD, T and Z scores were lower in the RN group in both the lumbar (p<0.01) and hip (p<0.05) regions.

Young male patients with hypercalciuric RN have lower BMD and higher bone turnover. Higher PTH levels related to vitamin D deficiency may contribute to bone demineralization in certain cases.
II. DOUBLE J STENTS

II.2.1. DOUBLE J STENT AND ACUTE REFLUX PYELONEPHRITIS

The double J stents are today an integrative part of urological activity all over the world. We cannot speak today about endourology without discussing about them. Unfortunately, a group of patients with such a stent inserted say that it is difficult to tolerate this device, feeling that the stent is, in fact, a “foreign body” and they ask for it to be removed at any cost.

Having more and more patients with double J stents inserted for different reasons (many of them to calm the colic from an impacted stone in the ureter), we have noticed that some with negative urine culture after the insertion return to the clinic with fever and sometimes lumbar pain. We have analyzed their situation in an article: CAN RECURRENT REFLEX ACUTE PYELONEPHRITIS BE PREVENTED IN PATIENTS WITH JJ URETERAL STENT AFTER DISCHARGE?, published in Archives of Biological Science, vol. 66, 4 (2014).

If the mechanism of producing this complication can be explained from the reality of impairing the anti-reflux mechanism by the stent itself, we could not have a general explanation about the pattern.

We focused on 84 cases that developed acute reflux pyelonephritis after days/weeks from discharge. We targeted the following aspects:
- cause for the insertion of double J stent;
- prior attempts of failed or successful catheterization;
- fever at the moment of insertion;
- urine chemical examination;
- place of residence (urban/rural) with regard to the conditions of hygiene;
- renal function at the time of JJ insertion;
- the degree of anemia, the number of leukocytes;
- urine culture;
- period of admission;
- the difficulty during catheterization (a difficult catheterization produces aggressive trauma - 67% patients were in this situation);
- associated pathology (can influence to a certain extent the appearance and maintenance of the inflammatory process either by lowering the body’s immune capacity, by affecting renal vasculature, or stressing the decline in renal perfusion).

The main reason for the insertion of the double J stent were the obstructive ureteral stones with intense recurrent pain or infected ureterohydronephrosis.

The data in Table 1. shows the predominance of this pathology for the age groups 60 - 69 years and 20 - 29 years with 17 cases each, followed by group 40 - 49 with 14 cases, then 50 - 59 years with 13 cases, group 30 - 39 with 11 cases, 70 - 79 years with 8 cases and, with only 2 cases each, 0 - 19 and 80 - 89 years.
Table 1. Patient distribution according to age

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Frequency</th>
<th>Percentage</th>
<th>Cumulative Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-19 years</td>
<td>2</td>
<td>2.4%</td>
<td>2.4%</td>
</tr>
<tr>
<td>20-29 years</td>
<td>17</td>
<td>20.2%</td>
<td>22.6%</td>
</tr>
<tr>
<td>30-39 years</td>
<td>11</td>
<td>13.1%</td>
<td>35.7%</td>
</tr>
<tr>
<td>40-49 years</td>
<td>14</td>
<td>16.7%</td>
<td>52.4%</td>
</tr>
<tr>
<td>50-59 years</td>
<td>13</td>
<td>15.5%</td>
<td>67.9%</td>
</tr>
<tr>
<td>60-69 years</td>
<td>17</td>
<td>20.2%</td>
<td>88.1%</td>
</tr>
<tr>
<td>70-79 years</td>
<td>8</td>
<td>9.5%</td>
<td>97.6%</td>
</tr>
<tr>
<td>80-89 years</td>
<td>2</td>
<td>2.4%</td>
<td>100%</td>
</tr>
<tr>
<td>Total</td>
<td>84</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

The average age of the patients was 47.64 (standard error = 1.945), the most common age was 42 years (standard deviation = 17.828), the minimum age was 19 years, the maximum age was 87. The status of the immune system should be taken into account, as well as personal body hygiene (Giannarini et al., 2011). Therefore, a potentially important aspect was the distribution of patients according to their place of residence. Contrary to our expectations of lower hygiene in rural areas, we observed that the pathology predominated in patients from urban areas. Thirty-five patients with acute reflux pyelonephritis were from rural areas and 49 of were from urban areas.

We also performed a distribution of cases depending on the etiology of obstruction for which the double J catheter insertion was practiced (Table 2). In order of prevailing importance for the obstruction, for which catheterization and insertion of double J stent were performed, there are: lithiasis, followed by pregnancy, congenital HN, tumor invasion/compression, stenosis, retroperitoneal fibrosis, retroperitoneal phlegmon, etc. Out of the total cases, for 3 of these the cause of obstruction wasn’t identified.

Table 2. The distribution of cases depending on the etiology of obstruction for which the JJ catheter insertion was carried out

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Frequency</th>
<th>Percentage</th>
<th>Cumulative Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithiasis</td>
<td>58</td>
<td>69.9%</td>
<td>69.9%</td>
</tr>
<tr>
<td>Pregnancy with hydronephrosis</td>
<td>6</td>
<td>7.2%</td>
<td>77.1%</td>
</tr>
<tr>
<td>Congenital hydronephrosis</td>
<td>5</td>
<td>6.0%</td>
<td>83.1%</td>
</tr>
<tr>
<td>Tumoral compression/invasion</td>
<td>4</td>
<td>4.8%</td>
<td>88.0%</td>
</tr>
<tr>
<td>Stenosis</td>
<td>3</td>
<td>3.6%</td>
<td>91.6%</td>
</tr>
<tr>
<td>Unspecified cause</td>
<td>3</td>
<td>3.6%</td>
<td>95.2%</td>
</tr>
<tr>
<td>Meanderings</td>
<td>1</td>
<td>1.2%</td>
<td>96.4%</td>
</tr>
<tr>
<td>Retroperitoneal fibrosis</td>
<td>2</td>
<td>2.4%</td>
<td>98.8%</td>
</tr>
<tr>
<td>Retroperitoneal phlegmon</td>
<td>1</td>
<td>1.2%</td>
<td>100%</td>
</tr>
<tr>
<td>Total</td>
<td>83</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>
Ureteral catheterization is a trauma for the ureterovesical junction and, in particular, the ureteral orifice (Ringel et al., 2000). We observed an increase of spontaneous calculi eliminations in a significant percentage of the patients with ureteral lithiasis (61%). This could suggest that the crossing of the calculi through the junction could have resulted in lesions affecting the antireflux mechanism. Until now there was no discussion on the length/size of the loop of the double J probe left inserted in the bladder. We use stents that are available in the emergency unit; however, stents should be linked to the patient’s height. Thus, a stent that is too long could favor germ migration in renal parenchyma, causing infection and forcing patients to return to the clinic.
II.2.2. DOUBLE J STENTS AND THE QUALITY OF LIFE

In the paper: **MORBIDITY AND IMPACT ON QUALITY OF LIFE IN PATIENTS WITH INDWELLING URETERAL STENTS: A 10 YEAR CLINICAL EXPERIENCE**, published in the *Pakistan Journal of Medical Sciences*. 2015; 31(3):522-6. doi: 10.12669/pjms.313.6759, with a group of urologist from the University of Brasov, Romania, we have analyzed the evolution of the patients with double J stents for a 10 year period. We used two questionnaires to evaluate the way patients tolerate these stents: Flanagan Quality of Life Scale (QOLS) with 16 items and our own questionnaire which was not validated yet.

Patients who required double J stent (DJS) placement were aged between 18 and 84 years. In all cases the informed consent was obtained before performing any urological procedures and all ethical procedures and protocols from our hospital were followed. The way of placing DJS was generally retrograde using the cystoscope or subsequent to performing retrograde ureteroscopy. In some cases, the stent placement has been made in open surgery. We always tried to maintain the stent over a small period of time, considering possible complications of the internal urinary drainage. Within the protocol we included QOLS (16 items) and a not-validated questionnaire developed by the team members, which followed the concentration of parameters with urologic significance that must be followed, in terms of the presence and degree of severity. Within this questionnaire varying degrees of the following clinical parameters were observed: urinary frequency, dysuria, urgency, suprapubic pain, radiating lumbar pain, macroscopic haematuria. Signs and symptoms were ranked from 1 (no or minimal) to 5 (maximum intensity).

The questionnaires were given to patients in three distinct moments of time: before DJS placement, 7 days from DJS placement and 14 days after the DJS removal; the results were analyzed according to the composition material of every stent used. In QOLS the scores range is between 16 and 112 (average for healthy population is 90). High scores reflect an enhanced quality of life. In evaluation of the quality of life (QoL) for these patients we didn’t use Ureteral Stent Symptom Questionnaire validated by Joshi et al. in March 2003 because, at the start of our study, this was not available. For correct analysis of results we take into consideration only the cases where we could apply the protocol proposed (1520 patients). All patients who were included in the study were followed prospectively and for statistical analyses we used SPSS soft.
Table 1. Distribution of cases according to indication of ureteral stent mounting

<table>
<thead>
<tr>
<th>PLACEMENT INDICATION</th>
<th>NO. PATIENTS</th>
<th>PERCENTAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>OBSTRUCTIVE ANURIA</td>
<td>264</td>
<td>12%</td>
</tr>
<tr>
<td>AFTER URETEROSCOPY</td>
<td>748</td>
<td>34%</td>
</tr>
<tr>
<td>PUSH-BACK OF SUPERIOR URETERAL STONES</td>
<td>176</td>
<td>8%</td>
</tr>
<tr>
<td>DJS IN OPEN SURGERY PROCEDURES:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- PYELOPLASTY</td>
<td>132</td>
<td>6%</td>
</tr>
<tr>
<td>- PIELOLITOTOMY</td>
<td>154</td>
<td>7%</td>
</tr>
<tr>
<td>- URETEROLITHOTOMY</td>
<td>44</td>
<td>2%</td>
</tr>
<tr>
<td>ONCOLOGIC DISEASES</td>
<td>418</td>
<td>19%</td>
</tr>
<tr>
<td>BEFORE PERFORMING ESWL</td>
<td>66</td>
<td>3%</td>
</tr>
<tr>
<td>EMERGENCY INTERNAL URINARY DRAINAGE</td>
<td>198</td>
<td>9%</td>
</tr>
</tbody>
</table>

Out of 2,200 patients with indwelled ureteral stent, 61.63% (n=1,356) were males and 38.36% (n=844) were females. The stent retaining period was between 5 and 218 days, with an average of 31 days. We used 6-7 Ch. stents, with a length of 24 - 28cm. Distribution of cases according to the composition of stent was: aliphatic polyurethane (40.98%), hydrophilic polyurethane coating (20.72%), carbothane (17.82%), silicon (20.46%). The choosing of stent was random, depending on stents available in our clinic at that time, with exception of patients who required long time internal urinary drainage for whom the use of "long-life" stents (carbothane) was taken into account. In Tables 2, 3 and 4 we present the results from our data.

Table 2. Results obtained after applying of our not-validated questionnaire

<table>
<thead>
<tr>
<th></th>
<th>Before stent indwelling</th>
<th>At 7 days after the indwelling of stent</th>
<th>After removal of the stent (14 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>0.48%</td>
<td>0.95%</td>
<td>1.47%</td>
</tr>
<tr>
<td>Dysuria</td>
<td>2.24%</td>
<td>3.17%</td>
<td>2.21%</td>
</tr>
<tr>
<td>Suprapubic pain</td>
<td>5.77%</td>
<td>8.88%</td>
<td>5.16%</td>
</tr>
<tr>
<td>Urgency</td>
<td>1.92%</td>
<td>1.9%</td>
<td>2.95%</td>
</tr>
<tr>
<td>Lumbar pain</td>
<td>13.8%</td>
<td>18.4%</td>
<td>18.81%</td>
</tr>
<tr>
<td>Macroscopic haematuria</td>
<td>1.92%</td>
<td>2.22%</td>
<td>3.32%</td>
</tr>
<tr>
<td>Persistent</td>
<td>1.28%</td>
<td>1.58%</td>
<td>5.16%</td>
</tr>
</tbody>
</table>

Legend: A - aliphatic polyurethane; B - hydrophilic polyurethane coating; C - carbothane; D - silicone; *p<0.05
Table 3. Results obtained from QOLS

<table>
<thead>
<tr>
<th></th>
<th>Before indwelling stent</th>
<th>At 7 days after the indwelling of stent</th>
<th>After removal of the stent (14 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (average)</td>
<td>Standard deviation</td>
<td>Mean (average)</td>
</tr>
<tr>
<td>Aliphatic polyurethane (n=623)</td>
<td>88,74</td>
<td>19,24</td>
<td>68,03</td>
</tr>
<tr>
<td>Hydrophilic polyurethane coating (n=315)</td>
<td>88,24</td>
<td>16,85</td>
<td>69,13</td>
</tr>
<tr>
<td>Carbothane (n=271)</td>
<td>62,89</td>
<td>14,65</td>
<td>59,67</td>
</tr>
<tr>
<td>Silicone (n=311)</td>
<td>86,98</td>
<td>16,73</td>
<td>79,67</td>
</tr>
</tbody>
</table>

Table 4. Distribution of cases by the complications after indwelling the DJS

<table>
<thead>
<tr>
<th>Complication</th>
<th>Percentage</th>
<th>Comments</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>9,01% (n=137)</td>
<td>no severe</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>6.11% (n=93)</td>
<td>evolution favorable</td>
<td></td>
</tr>
<tr>
<td>Malposition</td>
<td>0,98% (n=15)</td>
<td>solved by removing stent</td>
<td></td>
</tr>
<tr>
<td>Superior or inferior ureteral migration</td>
<td>4.01% (n=61)</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Inadequate relief of obstruction</td>
<td>20.72% (n=315)</td>
<td>17.82% stent replacement was required</td>
<td></td>
</tr>
<tr>
<td>Encrustation (See Fig. 1, 2 and 3)</td>
<td>15% (n=228)</td>
<td>4 cases (0,92%) – ESWL</td>
<td>6 cases (0,39%) ureteroscopy or cystolitholapaxy</td>
</tr>
<tr>
<td>Stent fracture</td>
<td>1,11% (n=17)</td>
<td>removal of stent fragments</td>
<td></td>
</tr>
<tr>
<td>Ureteral erosion or fistulization</td>
<td>no</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Forgotten stent</td>
<td>0,19% (n=3)</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Stenturia</td>
<td>no</td>
<td>no</td>
<td></td>
</tr>
</tbody>
</table>

It is obvious in this 10 year prospective study that the presence of DJS causes varying degrees of discomfort to patients. The analysis of data revealed statistically insignificant differences between the 4 types of stent used. None of the materials proved to be superior in terms of secondary manifestations for this foreign body in the urinary tract.

Urinary frequency and urgency are symptoms directly caused by mechanical factor. The majority of patients complain that these symptoms increased significantly during the day, highlighting the dependency on physical activity. Bladder muscle over activity is clearly enhanced by the presence of DJS. The urinary frequency and urgency were present in significant statistical percentage 7 days after the stent placement (p<0.05).

Dysuria seems to be more common when using stents with excessive length; in this study dysuria appeared in statistically significant proportion (p<0.05) at 7 days after stent placement and remain after its removal, but without statistical significance in this case. Suprapubic pain is caused by direct irritation of the bladder mucosa determined by the stent, but can be exacerbated in the case of secondary infection or stones in the distal volute. In our study this is obviously more common after mounting the stent, but statistically insignificant in this group, and in a relative similar percentage to the base value 14 days after stent removal.

Back pain is caused by vesicoureteral reflux, being secondary to the temporary cancellation of the intramural antireflux mechanism. We observed a clear increase but not a
A statistically significant incidence of back pain. 

Haematuria is a very common sign, being dependent mainly by physical activity, by mucosal microtrauma. Single episode or intermittent haematuria was present in a statistically significant percentage of patients with DJS and persisted at 14 days after stent removal (but not significant). Persistent haematuria highlighted a statistically significant increase in patients with DJS, after suppressing of internal drainage the percentage approaching the base value.

As regards to stent complications like urinary tract infection, encrustation, migration, spontaneous fracture, malposition, inadequate relief of obstruction or forgotten stent, our results are relatively similar to those in the literature. Regarding the results of QOLS, mean scores before the stent was placed were relative similar (close to 90), except the cases were a carbothane stent was used (majority with cancer), when the quality of life is profoundly affected due to the disease itself. At 7 days after stent placement, mean scores show a clear reduction in the QoL for those patients, but at 14 days after its suppression the average scores are somewhat closer to the baseline. In all cases the standard deviation was at a great value, indicating a high variability of responses, reflecting the different ability of patients to cope with distressing symptoms caused by this foreign body. Our results further contribute to studies of other authors. Thus, during stenting period there was noticed a significant percentage of sleep disorders, anxiety, decreased of libido and other sexual dysfunction, 45% of patients reporting reduced quality of life; Joshi demonstrated a reduction by 80% of quality of life in patients with DJS [46].

Although it is a real success of modern technology and the element that, in many cases, helped us save the kidney, DJS may cause some side effects and impaired quality of life of patients that are not neglected. Our study, that was conducted on a large number of patients, followed prospectively, brings many elements that show a statistically significant increase in the incidence of numerous side effects and impaired QoL, further contributing to the existing data from the literature as regards the knowledge of the pathology determined by the presence of foreign body in the urinary tract. Although most of the complications caused by the stent do not threaten the patient’s life, it is the duty of those involved in their care to bring more information and results from their experiences and contribute in finding innovative solutions. The use of ureteral stents, even if they are not “ideal”, is indispensable in modern urology.
II.2.2. THE INFLUENCE OF THE DOUBLE J STENTS OVER THE RESULTS OF ESWL

Another study elaborated in order to evaluate the impact of double J stents was:

The key to success for fragmenting a stone with the help of the shock waves, is dependent of a free path from the source (the lithotripter) to the target. On the other hand, the placement of a stent in an emergency situation for intense pain is a usual occurrence in urological departments. At the same time, the stent can mobilize the stone and push it back in the pielocaliceal system.

This prospective study involved 162 consecutive adult patients with pelvic renal stones treated by ESWL that fulfilled all the following inclusion criteria: single pelvic renal stone, < 15mm, visible on plain kidney-uretero-bladder X-ray (KUB), with double J stent and without prior ESWL treatment on the same side. Exclusion criteria were represented by the contraindications for ESWL (pregnancy, coagulation disorders, aortic aneurysm and platelet aggregation inhibitors). The pelvic renal stones were either primary located in the renal pelvis or secondary to retrograde stone mobilization from the ureter. Double J stents were inserted for impacted pelvic renal stone or after the retrograde mobilization of the stone from the ureter. The inclusion period was June 2001 - January 2015.

Before the insertion of JJ stent, the functional evaluation of the obstructed kidney for all patients was performed using intravenous urography (IVU). The patients were included in one of the three groups, based on KUB deemed relation between the stone and upper loop of the stent: group A – stone inside loop, group B – loop crossing stone and group C- stone outside loop. The stone density, as revealed by KUB, was classified as intense radiopaque (IR: opacity similar to the 12th rib or higher), moderate radiopaque (MR: opacity lower than the 12th rib) and slightly radiopaque (SR: stone barely visible). For preoperative assessment of stone opacity, KUB was evaluated by two radiologists and, in the case of no consensus, a third opinion was used to deem the stone as IR, MR or SR. The double J stent (Fr 6, Fr 7 or Fr 8 in caliber) was previously inserted, in each case, only for emergency reasons: recurrent renal colic refractory to medical treatment or renal colic with obstructive stone and fever. All stent insertions were uneventful, leading to stone migration to the renal pelvis. In case of urinary tract infection, antibiotics were prescribed prior, only patients rendering sterile urine status being subject to ESWL treatment.

ESWL was performed by the same urologist, having an experience of more than 1500 procedures, using a Chinese second generation spark gap lithotripter, model KS 88-4, with radiologic targeting system, 18kV and a standard procedure of 3000 shock waves per session. A second and a third session were used as standard protocol at 3 - 4 weeks interval, when the stone free status had not been rendered. Patients from the study groups were evaluated monthly for at least 1 month. If they achieved the stone free status they would exit the study group. Patients who did not render the stone free status were treated in a second and, eventually, a third session. After 3 months from the 3rd ESWL session, an alternative treatment was chosen. The follow-up of the patients included KUB and ultrasound
examination at 3 - 4 weeks post ESWL. The results were deemed as: stone-free (SF) - when no visible residual fragments were found on KUB and US, stone fragments (F) - when fragments of any dimension lower than the original stone size, including those smaller than 4 mm were found, or stone not fragmented (NF) - when the stone size had the same dimensions as before treatment. In order to avoid biases, postoperative evaluations were performed by the same experienced investigators.

Two investigators were involved: one radiologist for KUB, unknowledgeable to ultrasound results and one urologist for ultrasound, uninformed of the KUB results. In case of the lack of concordance between results, a case review and consensus meeting was imposed, by allowing both investigators to see all the imagistic evaluations. If stone-free status was not obtained on KUB and ultrasound investigations, a second and if necessary a third ESWL was performed. A multivariate analysis regarding the influence upon ESWL efficiency for stone radio-opacity (IR, MR or SR, respectively), stone size (< 10 and 10 – 15 mm), BMI as dened by the World Health Organization (normal weight BMI 18.5 – 25, overweight BMI 25 – 30 and obese patients BMI >30) and double J stent caliber (6 Fr, 7 Fr or 8 Fr) was realized.

JJ stents were retrieved after rendering the stone free status, no later than 3 months from insertion or upon request. In case of stent intolerance Tamsulosin 0.4mg, once daily, was administered. After the completion of the study protocol, patients not reaching the stone free status were treated with PCNL, semirigid ureteroscopy for Steinstrasse or by retrograde intrarenal surgery (RIRS).

The mean age of the patients was 48 ± 3 years (range 25 – 64), without statistical differences between the three groups; male/female ratio was 1.53. Out of 162 patients, sixteen had the stent removed upon request, although they did not reach the stone free status after one (n = 5), two (n = 6), or three sessions (n = 5), because it was hard to tolerate despite Tamsulosin 0.4 mg/day for the whole period when they had the stent in place and Lornoxicam 8 mg/day for 10 days after each ESWL session. In order to avoid biases, these patients were excluded from the study. Twelve cases with opinion differences regarding the results of ESWL, as evaluated by KUB and ultrasound, were debated in order to achieve consensus.

Table 1 presents the other patient characteristics in the study groups, related to radio-opacity, BMI, stent caliber and stone size. There were no statistically significant differences between the three groups regarding the above mentioned characteristics. In each of the three groups, the percentage of obese patients was insignificant. The results of ESWL are presented in the left side of Tables 1, 2, 3 and 4, with the statistics for the relevant comparisons described in the right side of each table. The situation stone-inside-loop (group A) reduced ESWL overall success rate statistically significant comparing with group C (stone outside the loop) and with the overall results of group B and C combined (p=0.02 and p=0.004 respectively). For stone inside loop cases, ESWL efficiency was 22.7 %, about twice lower than 49.1% for the rest of cases (group B + C; p=0.002). ESWL success rate was ~ 3 times lower for stone located in the JJ stent loop after two sessions and remained ~ 2 times lower after the third session. Confidence levels were particularly high (p<0.01) for both the important comparisons directly relevant to the study main objective (A vs. C; A vs. B + C), regarding the endpoint frequency values for the stone-free status. We separately evaluated the influence of four other factors: stone radio-opacity, stone size, BMI and stent caliber. ESWL efficiency generally depended upon stone radio-opacity (Table 1.), BMI
(Table 2) or stent caliber (Table 3) but was not influenced by stone size. On univariate analysis, the stone density, as evaluated by KUB, influences the stone free status when comparing intense with slightly radiopaque stones, from the first ESWL session (p=0.045) and this trend maintain to the second session (p=0.044). Overall stone-free status is significantly lower in obese patients comparing the normal weight on a univariate analysis (p=0.013). Meantime, the larger the caliber of the ureteric JJ stent the smaller the chances of achieving stone-free status, regardless of the location of the stone relative to loop.

Table 1. Patient’s characteristics within the study group

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th></th>
<th>Group B</th>
<th></th>
<th>Group C</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>44</td>
<td>100</td>
<td>34</td>
<td>100</td>
<td>84</td>
<td>100</td>
</tr>
<tr>
<td><strong>Stone radio-opacity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR</td>
<td>15</td>
<td>34.1</td>
<td>12</td>
<td>35.3</td>
<td>29</td>
<td>34.5</td>
</tr>
<tr>
<td>MR</td>
<td>17</td>
<td>38.6</td>
<td>10</td>
<td>29.4</td>
<td>33</td>
<td>39.3</td>
</tr>
<tr>
<td>SR</td>
<td>12</td>
<td>27.3</td>
<td>12</td>
<td>35.3</td>
<td>22</td>
<td>26.2</td>
</tr>
<tr>
<td><strong>Stent caliber (mm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>27.3</td>
<td>8</td>
<td>23.5</td>
<td>14</td>
<td>16.7</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>22.7</td>
<td>3</td>
<td>8.8</td>
<td>10</td>
<td>11.9</td>
</tr>
<tr>
<td>6</td>
<td>22</td>
<td>50.0</td>
<td>23</td>
<td>67.6</td>
<td>60</td>
<td>71.4</td>
</tr>
<tr>
<td><strong>Body mass index (BMI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OB (BMI &gt;30)</td>
<td>3</td>
<td>6.8</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3.6</td>
</tr>
<tr>
<td>OV (BMI 25–30)</td>
<td>17</td>
<td>38.6</td>
<td>11</td>
<td>32.4</td>
<td>22</td>
<td>26.2</td>
</tr>
<tr>
<td>N (BMI 18.5–25)</td>
<td>24</td>
<td>54.5</td>
<td>23</td>
<td>67.6</td>
<td>59</td>
<td>70.2</td>
</tr>
<tr>
<td><strong>Stone size (mm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>23</td>
<td>52.3</td>
<td>15</td>
<td>44.1</td>
<td>33</td>
<td>41.7</td>
</tr>
<tr>
<td>10–15</td>
<td>21</td>
<td>47.7</td>
<td>19</td>
<td>55.9</td>
<td>49</td>
<td>58.3</td>
</tr>
</tbody>
</table>


Table 2. The ESWL outcome (case%) in the three groups and comparisons (chi square p values) among the study groups

<table>
<thead>
<tr>
<th>SWL outcome</th>
<th>Case %</th>
<th>p values</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>All</td>
<td>A versus B</td>
<td>A versus C</td>
</tr>
<tr>
<td>SF after 1st SWL</td>
<td>45</td>
<td>29</td>
<td>11.9</td>
<td>8.0</td>
<td>0.819</td>
<td>0.300</td>
</tr>
<tr>
<td>SF after 2nd SWL</td>
<td>45</td>
<td>14.7</td>
<td>25.0</td>
<td>17.3</td>
<td>0.247</td>
<td>0.009</td>
</tr>
<tr>
<td>SF after 3rd SWL</td>
<td>13.7</td>
<td>23.5</td>
<td>15.5</td>
<td>16.7</td>
<td>0.496</td>
<td>0.087</td>
</tr>
<tr>
<td><strong>Overall stone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>free</td>
<td>22.7</td>
<td>41.1</td>
<td>52.4</td>
<td>42.0</td>
<td>0.133</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Residual fragments</strong></td>
<td>36.4</td>
<td>23.4</td>
<td>27.4</td>
<td>30.9</td>
<td>0.897</td>
<td>0.597</td>
</tr>
<tr>
<td><strong>Stone not fragmented</strong></td>
<td>40.9</td>
<td>26.5</td>
<td>20.2</td>
<td>27.1</td>
<td>0.276</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Values in italics for p < 0.05
Group A: stone-inside-loop, Group B: loop-crossing-stone, Group C: stone-outside-loop, All: the whole study group, SF: stone-free
Table 3. The ESWL outcome (case%) according to stone ratio-opacity and comparisons (chi square p values) among the study groups

<table>
<thead>
<tr>
<th>SWL outcome</th>
<th>Case %</th>
<th>p values</th>
<th>IR versus MR</th>
<th>IR versus SR</th>
<th>IR versus other</th>
<th>SR versus MR</th>
<th>SR versus other</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF after 1st SWL</td>
<td>3.6</td>
<td>5.0</td>
<td>17.4</td>
<td>8.0</td>
<td>0.937</td>
<td>0.043</td>
<td>0.225</td>
</tr>
<tr>
<td>SF after 2nd SWL</td>
<td>10.7</td>
<td>16.7</td>
<td>26.1</td>
<td>17.3</td>
<td>0.510</td>
<td>0.044</td>
<td>0.165</td>
</tr>
<tr>
<td>SF after 3rd SWL</td>
<td>14.3</td>
<td>18.3</td>
<td>17.4</td>
<td>16.7</td>
<td>0.736</td>
<td>0.876</td>
<td>0.712</td>
</tr>
<tr>
<td>Overall stone free</td>
<td>28.6</td>
<td>40.0</td>
<td>60.9</td>
<td>42.0</td>
<td>0.272</td>
<td>0.002</td>
<td>0.019</td>
</tr>
<tr>
<td>Residual fragments</td>
<td>33.9</td>
<td>31.7</td>
<td>26.1</td>
<td>30.9</td>
<td>0.951</td>
<td>0.522</td>
<td>0.044</td>
</tr>
<tr>
<td>Stone not fragmented</td>
<td>37.5</td>
<td>28.3</td>
<td>13.0</td>
<td>27.1</td>
<td>0.394</td>
<td>0.010</td>
<td>0.049</td>
</tr>
</tbody>
</table>

Values in italics for p < 0.05
IR: Intense radiopaque (similar or superior to 12th rib opacity), MR: Moderate radiopaque (less opaque than 12th rib), SF: Slightly radiopaque (barely visible), SF: Stone free

Table 4. The ESWL outcome (case%) according to body-mass index (BMI) and comparisons (chi square p values) among the study groups

<table>
<thead>
<tr>
<th>SWL outcome</th>
<th>Case %</th>
<th>p values</th>
<th>OB versus OV</th>
<th>OB versus N</th>
<th>OB versus OV + N</th>
<th>N versus OV</th>
<th>N versus OB + OV</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF after 1st SWL</td>
<td>0</td>
<td>0</td>
<td>12.3</td>
<td>8.0</td>
<td>–</td>
<td>0.797</td>
<td>0.977</td>
</tr>
<tr>
<td>SF after 2nd SWL</td>
<td>0</td>
<td>6.0</td>
<td>23.6</td>
<td>17.3</td>
<td>0.732</td>
<td>0.598</td>
<td>0.555</td>
</tr>
<tr>
<td>SF after 3rd SWL</td>
<td>0</td>
<td>2.0</td>
<td>24.5</td>
<td>16.7</td>
<td>0.200</td>
<td>0.375</td>
<td>0.577</td>
</tr>
<tr>
<td>Overall stone free</td>
<td>0</td>
<td>8.0</td>
<td>60.4</td>
<td>42.0</td>
<td>0.905</td>
<td>0.013</td>
<td>0.035</td>
</tr>
<tr>
<td>Residual fragments</td>
<td>0</td>
<td>32.0</td>
<td>22.1</td>
<td>30.9</td>
<td>0.246</td>
<td>0.228</td>
<td>0.023</td>
</tr>
<tr>
<td>Stone not fragmented</td>
<td>0</td>
<td>60.0</td>
<td>7.5</td>
<td>27.1</td>
<td>0.139</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values in italics for p < 0.05
OB: Obese (BMI >30), OV: Overweight (BMI 25-30), N: Normal weight (BMI 18.5-25), SF: Stone Free

Our results seem to sustain the hypothesis that stone-inside-loop relation reduces the ESWL efficiency as an independent parameter on a multivariate analysis. In patients with single renal pelvic stone and JJ stent, the stone inside loop position lowers ESWL success. In correlation with other prognostic factors, the relative position of the stone to the JJ loop could be a helpful tool in choosing the most appropriate treatment for the patient, minimizing the discomfort and the costs. The overall stone-free rate, lower than the results published in the literature for the renal pelvic stones, could be explained by the second generation lithotripter we used for all procedures.
II.3. URINARY TRACT INFECTIONS

Urinary tract infections (UTIs) are common, affect men and women of all ages, and vary dramatically in their presentation and sequels. They are a common cause of morbidity and can lead to significant mortality.

DEFINITIONS:
UTI is an inflammatory response of the urothelium to bacterial invasion that is usually associated with bacteriuria and pyuria.

Bacteriuria is the presence of bacteria in the urine, which should normally be free of bacteria.

Pyuria, the presence of white blood cells in the urine, is generally indicative of infection and an inflammatory response of the urothelium to the bacteria.

INCIDENCE AND EPIDEMIOLOGY
UTIs are considered to be the most common bacterial infection and account for more than 7 million visits to the physician's offices, well over 1 million hospital admissions in the United States annually. French epidemiologic studies evaluated the annual incidence at 53,000/million persons per year, which represents 1.05% to 2.10% of the activity of general practitioners. It has been estimated that more than 50% of women will suffer one or more symptomatic urinary tract infection in their lifetime and 25% of patients who experience a UTI get recurrent infections.

The incidence of UTI is higher among females for whom it commonly occurs in an anatomically normal urinary tract. Conversely, in males and children, UTI generally reveals a urinary tract lesion that must be identified by imaging and should be treated to suppress the cause of infection and prevent recurrence.

ETIOLOGY AND PATHOGENESIS
The urinary tract is normally sterile above the distal urethra. Most UTIs are caused by bacteria (facultative anaerobes), usually originating from the bowel flora. UTIs are a result of interactions between the uropathogen and the host. Successful infection of the urinary tract is determined, in part, by the virulence factors of the bacteria, the inoculum size, and the inadequacy of host defense mechanisms. These factors also play a role in determining the ultimate level of colonization and damage to the urinary tract.

Most pathogens responsible for UTI are enterobacteriaceae with a high predominance of *E. coli*. This is especially true of spontaneous UTI in females (cystitis and pyelonephritis). Other strains are less common, including *Proteus mirabilis* and more rarely gram-positive microbes.

Bacterial uropathogenicity plays a major role in host-pathogen interactions that lead to UTIs. For *E. coli*, these factors include flagella necessary for motility, a pore-forming hemolysin and, above all, presence of adhesions on the bacterial fimbriae, as well as on the bacterial cell surface. As for *Proteus mirabilis*, it is endowed with other nonfimbrial virulence factors, including the property of secreting urease, which splits urea into NH3 and CO2.

There are three routes of infection: ascending route (from the bowel reservoir, vagina or perineal skin via ascent through the urethra into the bladder and then through the ureter to the renal pelvis and parenchyma), hematogenous route (with *Staphylococcus aureus*...
bacteremia originating from oral sites or with *Candida fungemia*) and lymphatic route (direct extension of bacteria from the adjacent organs).

On the other hand, there are predisposing factors, alterations in host defense mechanisms such as: obstruction to urine flow at all anatomic levels, vesicoureteral reflux, underlying conditions that cause chronic interstitial nephritis (diabetes mellitus, sickle cell disorders, adult nephrocalcinosis, hyperphosphatemia, hypokalemia, analgesic abuse, gout and aging), renal papillary necrosis, pregnancy, spinal cord injury.

**DIAGNOSIS:**

The diagnosis of UTI relies on urinalysis and urine culture. Most often, the urine is obtained from a voided specimen. In children who are not toilet-trained, a urine collection device, such as a bag, is placed over the genitalia and the urine is cultured from the bagged specimen. Suprapubic aspiration avoids potential contamination, however, due to its invasiveness, is rarely used except in children and selected patients.

The urine can be immediately evaluated for leukocyte esterase, a compound produced by the breakdown of white blood cells (WBCs) in the urine. Urinary nitrite is produced by reduction of dietary nitrates by many gram-negative bacteria. Esterase and nitrite can be detected by a urine dipstick. Microscopic examination of the urine for WBCs and bacteria is performed after centrifugation. A combination of these tests may help to identify those patients in whom urine culture will be positive.

The gold standard for identification of UTI is the quantitative culture of urine for specific bacteria. The urine should be collected in a sterile container and cultured immediately after collection. When this is not possible, the urine can be stored in the refrigerator for up to 24 hours. The number of colonies is counted and adjusted per milliliter of urine (CFU/mL). Traditionally, > 100,000 CFU/mL from a single bacterial type is used to exclude contamination. In a suprapubic bladder puncture specimen any count of bacteria is relevant. However, studies have clearly demonstrated that clinically significant UTI can occur with < 100,000 CFU/mL bacteria in the urine. The most common bacterial causes of UTI are: *E. Coli*, *Enterococcus*, *Proteus mirabilis*, *Klebsiella sp*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*.

In pregnancy, there are anatomic and physiologic changes to the urinary tract due to compression by the gravid uterus and alterations in the hormonal status. Renal length increases approximately by 1 cm during normal pregnancy as a result of increased vascular and interstitial volume. The glomerular filtration rate increases by 30 – 50%, most likely secondary to the increase in cardiac output. There is also significant ureteral dilation with resultant urinary stasis during the second and third trimesters of gestation. This is attributed to the smooth muscle–relaxing effects of progesterone and the mechanical compression of the ureters by the uterus at the level of the pelvic floor, the bladder is also affected. The enlarged uterus displaces the bladder superiorly and anteriorly. The bladder becomes hyperemic; the capacity is increased most likely due to the effects of progesterone.

Because of these changes in the urinary tract during normal pregnancy, bacteriuria is a clinically relevant finding in pregnant women. Asymptomatic bacteriuria is one of the most common infectious complications of pregnancy. It is estimated that the prevalence of bacteriuria is 4 - 6%, which is not significantly different from that in nonpregnant women of comparable age. Interestingly, approximately 30% of those who have bacteriuria on screening
evaluation, later develop pyelonephritis, compared to only 1 - 2% in those who do not have bacteriuria. Treatment of bacteriuria decreases the incidence of pyelonephritis during pregnancy to approximately 3%.

However, because women with asymptomatic bacteriuria are at higher risk for developing a symptomatic UTI that results in adverse fetal sequelae, complications associated with bacteriuria during pregnancy, and pyelonephritis with possible sequelae (sepsis in the mother), all women with asymptomatic bacteriuria should be treated.

Selection of an antimicrobial agent to treat the bacteriuria must be made, however, with special considerations given to maternal and fetal toxicity. Drugs that are relatively contraindicated during pregnancy include: fluoroquinolones, trimethoprim, chloramphenicol, erythromycin, tetracycline, sulfonamides and nitrofurantoin.

Pregnant women with acute pyelonephritis should be hospitalized and treated initially with parenteral antimicrobial agents (cephalosporin). More than 95% of these patients respond within 24 hours of using ampicillin or cephalosporins. Appropriate oral agents should then be given for at least 14 days: CEFTIBUTENE (CEDAX) 400mg/day, CEPHALEXIN 125mg/day or CEFACLOR 250mg/day.

UROSEPSIS AND SEPTIC SHOCK

Sepsis is a clinical syndrome characterized by extremes of body temperature, heart rate, respiratory rate and white blood cell count, that occurs in response to an infection. Sepsis occurs when a local infectious process becomes an uncontrolled systemic blood borne inflammatory response resulting in damage to the tissue or organs remote from the initial site of infection or injury.

Definitions:
- Bacteremia: the presence of viable bacteria in the blood;
- Systemic inflammatory response syndrome (SIRS): a clinical syndrome characterized as extremes of body temperature, heart rate, ventilation and immune response;
- Sepsis: SIRS and infection either documented or strongly suspected;
- Septic shock: an extreme form of sepsis complicated by organ dysfunction and persistent circulatory failure despite fluid and pharmacologic resuscitation.

Early signs of the systemic inflammatory response syndrome include temperature extremes (> 38° C or < 36° C), tachycardia (heart rate > 90 beats/minute), tachypnea and altered mental status. Other diagnostic criteria include evidence of organ dysfunction such as hypotension, oliguria or ileus and laboratory abnormalities (leucocytosis/leukopenia, hyperbilirubinemia, hyperlactatemia, hyperglycemia, coagulation abnormalities and elevated C reactive protein and procalcitonin.

The classic clinical presentation of gram-negative bacteremia is with fever and chills followed by hypotension. Even before temperature extremes and the onset of chills, bacteremic patients often begin to hyperventilate. Thus, the earliest metabolic change in septicemia is a resultant respiratory alkalosis. Changes in mental status can also be important clinical clues. Although the most common pattern is lethargy or obtundation, an occasional patient may become excited, agitated, or combative. Cutaneous manifestations such as the “bull's-eye” lesion associated with Pseudomonas aeruginosa may be identified.

The principles of management of sepsis include resuscitation, supportive care, monitoring, administration of broad-spectrum antimicrobial agents and drainage or elimination of infection.
II.3.1. INFECTED HYDRONEPHROSIS

One of the most frequent complications of renal and ureteral lithiasis, mostly, but also for other urologic pathologies, which can affect the life of the patient, is infected hydronephrosis. So we have decide to analyze different aspects of this life-threatening situation on different aspects and we published the results in the article: INFECTED HYDRONEPHROSIS: CAN WE REDUCE PATIENT SUFFERING AND COSTS? in J Pak Med Assoc. 2016 Nov; 66(11):1372-1377.

Hydronephrosis and, even more, infected hydronephrosis, are urologic emergences and so the life of the patient depends on the moment he addresses the urologist in order to drain the infected urine. This multicentric, retrospective study was conducted in three Romanian academic urology departments from “Dr. C. I. Parhon” Clinic Hospital Iasi, Targu Mures County Hospital, "Prof. Dr. Th. Burghele" Clinical Hospital Bucharest and comprised data of patients with infected hydronephrosis treated between 1.07.2013 and 1.07.2014. The diagnosis was based on clinical evidence of the systemic inflammatory response syndrome (SIRS) and ultrasonographic evidence of hydronephrosis. Clinical data, comorbidities and hydronephrosis etiology were analyzed. The outcomes measured included type of procedure, admission to intensive care unit (ICU), length of hospital stay and hospitalization costs.

Based on the hospitalisation costs (number of days, drugs and specific materials) the data of patients was divided into three groups: group A - cost/patient less than 500 euros, group B - cost/patient between 500 and 1.000 euros and group C - cost/patient over 1.000 euros. The monetary figures mentioned above were spent on the treatment of the acute infected hydronephrosis episode. Many of the patients were discharged after being stabilized and readmitted at a later date in order to ascertain the cause of the infected hydronephrosis.

All of the patients benefited from a renal drainage through PNS or JJ insertion. Using JJ stents was the first choice and PNS insertion was employed from the beginning in cases with hydronephrosis due to cancer, compression on the urogenital tract, failure of JJ insertion. The study was approved by the ethical review boards of the participant institutions.

Statistical analysis was performed using Chi-Square test and student's t-test (two samples assuming unequal variances) in Microsoft Office Excel 2010. P<0.05 was considered statistically significant.

Of the 175 patients, there were 49 (28%) in group A, 95 (54.3%) in group B and 31 (17.7%) in group C. Besides, 35 (71.42%) patients had fever in group A compared to 60 (63.15%) in group B and 19 (61.29%) in group C (Table 1.).
Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>49</td>
<td>95</td>
<td>31</td>
</tr>
<tr>
<td>Age</td>
<td>59.02±17.95</td>
<td>57.64±19.91</td>
<td>54.90±17.49</td>
</tr>
<tr>
<td>Gender Male : Female</td>
<td>14:33</td>
<td>30:65</td>
<td>9:22</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>31 (71.42%)</td>
<td>60 (63.15%)</td>
<td>19 (61.29%)</td>
</tr>
<tr>
<td>Chills</td>
<td>33 (67.34%)</td>
<td>56 (58.94%)</td>
<td>19 (61.29%)</td>
</tr>
<tr>
<td>Pain only</td>
<td>14 (28.57%)</td>
<td>25 (26.39%)</td>
<td>7 (22.59%)</td>
</tr>
<tr>
<td>US modified echogenicity</td>
<td>13 (30.69%)</td>
<td>24 (25.69%)</td>
<td>11 (35.48%)</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>30 (61.22%)</td>
<td>58 (61.05%)</td>
<td>30 (96.79%)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>16 (32.69%)</td>
<td>52 (54.78%)</td>
<td>24 (77.41%)</td>
</tr>
<tr>
<td>Ecology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lithiasis</td>
<td>7 (14.29%)</td>
<td>7 (7.13%)</td>
<td>5 (16.05%)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>16 (32.69%)</td>
<td>4 (4.16%)</td>
<td>6 (19.35%)</td>
</tr>
<tr>
<td>UPO*</td>
<td>8 (16.00%)</td>
<td>4 (4.16%)</td>
<td>9 (29.03%)</td>
</tr>
<tr>
<td>Urogenital cancers</td>
<td>2.65%</td>
<td>8.42%</td>
<td>13.90%</td>
</tr>
<tr>
<td>Ureteral stenosis</td>
<td>2.65%</td>
<td>11.59%</td>
<td>12.90%</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (18.36%)</td>
<td>20 (21.01%)</td>
<td>3 (9.67%)</td>
</tr>
<tr>
<td>Obesity</td>
<td>9 (18.36%)</td>
<td>14 (14.23%)</td>
<td>2 (6.45%)</td>
</tr>
<tr>
<td>ATB before admission</td>
<td>Total</td>
<td>Self</td>
<td>GP</td>
</tr>
<tr>
<td></td>
<td>12 (24.49%)</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Moment of drainage (hours)</td>
<td>9.1</td>
<td>15.75</td>
<td>A vs. B p=0.027</td>
</tr>
</tbody>
</table>

*UPO: urethrostomy with obstruction
ATB: Antibiotics
GP: General practitioner.

Fever had no influence upon the costs (p=0.43), nor did diabetes (p=0.36).
Age was an element which influenced the costs (Table 2.)

Table 2. Evolution stay and costs

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evolution</td>
<td>Sim*</td>
<td>Com**</td>
<td>Death</td>
</tr>
<tr>
<td>Hospital stay</td>
<td>63 days</td>
<td>6.19 days</td>
<td>A vs B p=0.001</td>
</tr>
<tr>
<td></td>
<td>JJ</td>
<td>PNS p value</td>
<td>JJ</td>
</tr>
<tr>
<td></td>
<td>3.66 ± 0.12</td>
<td>6.17 ± 0.48</td>
<td>p=0.09</td>
</tr>
<tr>
<td>Total cost (euro)</td>
<td>352.77</td>
<td>606.29</td>
<td>NS</td>
</tr>
<tr>
<td>ATB cost (euro)</td>
<td>118.48</td>
<td>297.47</td>
<td>A vs B p=0.001</td>
</tr>
</tbody>
</table>

*Sim = evolution simple without hemodynamic instability
**Com = evolution complicated with hemodynamic instability and admission to intensive care unit
ATB: Antibiotics
PNS: percutaneous nephrostomy
NS: Not significant.

The mean age was 59.02 ± 17.95 years in group A, 57.64 ± 19.01 in group B and 54.90 ± 17.49 in group C. The total antibiotic cost was 26.92 euros per patients in group A compared with 67.60 euros in group B (p=0.0001) and 94.82 euros in group C (p=0.02).

The mean time spent between hospital admission and intervention was 9.1±3.64 hours in group A, 15.75 ± 8.18 hours (p=0.027) in group B, and 39.25 ± 12.03 hours (p=0.008) in group C. The duration of hospitalization was correlated with the final costs of hospitalization and the moment of drainage. Another element that influenced the patient’s evolution was the
moment of drainage ($p<0.05$). In cases of favourable evolution, the drainage was performed in a mean time of $5.88 \pm 2.71$ hours from the admission versus $7.44 \pm 3.62$ hours in cases of patients with unfavourable evolution ($p=0.005$).

The presence of renal insufficiency also influenced the costs and the duration of hospitalisation. In group A, 16 (32.6%) patients had renal insufficiency, while in group B and C there were 52 (54.7%) and 24 (77.41%) patients with azotaemia ($p=0.003$).

Moreover, there were 30 (61.22%) patients with leukocytosis in group A, 58 (61.05%) in group B and 30 (96.7%) in group C ($p=0.048$).

The mean hospitalisation duration for group A patients was $4.25 \pm 1.32$ days compared with $6.19 \pm 1.92$ days ($p=0.001$) for group B and $12.03 \pm 2.32$ days ($p=0.001$) for group C.

Mean hospitalisation cost was $600.53 \pm 85.11$ euros for JJ stent and $680.11 \pm 115.25$ euros for PNS. Patients with a favourable evolution had a mean age of $59.86 \pm 16.24$ years, while for those with an unfavourable evolution this figure stood at $62.78 \pm 17.69$ years. A negative prognostic factor was the recurrence of lithiasis and the neoplastic etiology ($p=0.001$) (Table 13).

**Table 13. Risk factors for complicated evolution**

<table>
<thead>
<tr>
<th></th>
<th>Sim</th>
<th>Com</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>119</td>
<td>56</td>
</tr>
<tr>
<td>Average age (years)</td>
<td>59.86</td>
<td>62.78</td>
</tr>
<tr>
<td>Neoplastic etiology</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>42.01%</td>
<td>76.78%</td>
</tr>
<tr>
<td>Moment of the intervation (hours)</td>
<td>5.88</td>
<td>17.44</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>58.82%</td>
<td>94.64%</td>
</tr>
<tr>
<td>Drainage method (JJ stent)</td>
<td>72.26%</td>
<td>27.74%</td>
</tr>
<tr>
<td>Drainage method (PNS)</td>
<td>59.61%</td>
<td>40.39%</td>
</tr>
</tbody>
</table>

*Sim - evolution simple without haemodynamic instability
**Com - evolution complicated with haemodynamic instability and admission to intensive care unit
PNS: Percutaneous nephrostomy.

It is obvious that infected hydronephrosis is one of the major emergencies in urological practice. It requires rapid drainage and efficient antibiotherapy in order to reduce the patient's suffering, the costs of the hospitalisation, and to shorten the length of hospitalisation. Although these facts are well known, in daily practice we are confronted frequently with situations that delay the moment of treatment and increase the costs. Urosepsis accounts for 25% of total sepsis — the majority of these situations result from ureteral stone obstruction. In our study, we found that urolithiasis was responsible for obstruction in 68.57% of all cases.

The diagnosis in cases of ureterohydronephrosis is immediate and non-invasive, as ultrasonography has a specificity of 100%. Nowadays, the use of ultrasound is widespread, with many general practitioners using the method in daily practice. In cases of hydronephrosis, a well-trained uroradiologist with a last generation ultrasound machine is capable of differentiating the modified echogenity from the normal one. Indeed, this step is crucial in the diagnosis. In our study, the percentage of the patients with modified echogenity was significantly higher than for the group with no changes (92.6% versus 64.1%; $p=0.03$).

In our study, 93.71% of the cases mentioned lumbar pain as the leading symptom, also the factor which made them present for a consult; only 65.71% presented with fever and
63.42% presented with chills as associated symptoms. The empirical antibiotherapy of a urinary tract infection associated with lumbar pain in the absence of fever and chills, leads to diagnostic difficulties from the point of view of a urologist working at the emergency department.

Self-medication and general abuse of antibiotics in recent years have given rise to important problems in public health, furthermore these occurrences are also responsible for increasing antibiotic resistance. In many of the cases, patients had begun the antibiotherapy prior to a specialist consultation, only based upon recommendations from friends or family. In many countries, local policies limit the use of antibiotics, but in our country there is no requirement for medical prescription. In well-developed countries, self-medication is between 8-13%, while in poorly developed countries it can reach 73%. There are also cases in which a specialist prescribes an antibiotic with an insufficient dosage or for a reduced period.

A falsely improved clinical picture can create difficulties for the urologist and make him or her reluctant to select an invasive drainage gesture. In the absence of some "mathematical" criteria and with the patient urging the specialist to select a non-invasive treatment, sometimes the decision is extremely difficult for the urologist. An old patient, with a history of lithiasis, has a high risk of developing urosepsis, with age representing a negative prognostic factor. In our study, age was a factor, and also had an impact upon costs.

Laboratory findings are very important in the evolution of patients with infected hydronephrosis. The presence of renal insufficiency and leukocytosis has a negative influence on the patients evolution. Surprisingly, diabetes had no negative impact upon evolution, with our data similar to that presented in literature. Furthermore, 33 patients (18.85%) suffering from diabetes did not necessitate additional costs compared with non-diabetic patients.

Patients and general practitioners need to understand that the most important moment in the management of these patients is the renal drainage (JJ stent or PNS); otherwise, the mortality increases alarmingly. A key factor in the evolution of these patients is the moment of drainage; the sooner the drainage occurs, the better. Indeed, rapid drainage leads to a more favourable evolution, and lower costs.

Despite the fact that urolithiasis is a multidisciplinary pathology, general practitioners play the most essential role in simplifying and optimising the management of lithiasis. It is obvious that in this pathology the general practitioner has a key role, underlined by duties that include diagnosis of the urolithiasis; sending the patient to the urologist as soon as possible in order to have immediate and specific treatment administered; following up the patients and offering them support for further treatment procedures like extracorporeal shock wave lithotripsy (ESWL), ureteroscopy, JJ reinsertion, conservative treatment; and following up on the compliance of patients regarding dietary regime, and identifying recurrences knowing that these can be frequently asymptomatic.

Pregnancy represents a particular situation, as these women cannot be investigated or treated by means of radiology. Any pregnant woman with signs of urological disease must be urgently sent to a urologist, while we feel that pregnant women with a history of lithiasis should have at least a urological consultation during pregnancy. In our study, 8 pregnant women had a lithiasic history, with only 3 of them requiring endourological procedures after delivery. Urolithiasis is one of the main non-obstetrical causes of hospital admission in cases of pregnant women. Identifying pregnant women with lithiasis is important not only from a urological point of view, but also given the fact that it is frequently associated with
preeclampsia, hypertension and diabetes, thus necessitating caesarean delivery. Despite the fact that lithiasis has an increasing frequency among the population, it remains constant among pregnant women. From the same point of view, urinary infection in pregnant women should be identified and treated even if they are asymptomatic. In every case, a pregnant woman should have a urine culture in the first three months. Because of urine features in case of pregnancy, the renal drainage must be strictly followed up, as they represent a high risk of calcification, even requiring additional procedures, reinsertions and more costs. Generally speaking, pregnant women do not tolerate the stents very well, as they represent a source of infection; indeed, the biofilm does not let the antibiotics penetrate. In the case of JJ stent or nephrostomy substitution there is a risk that these germs will reach the bloodstream.
II.3.2 MULTI DRUG RESISTANT URINARY TRACT INFECTIONS IN MOLDOVA

In fact, the urinary tract infections (UTI) and more of that multi drug resistant urinary tract infections (MDR-UTI) are a concern for the present and for next generations and Romania is in a particular situation: we are on the second place in Europe at the antibiotic use, after Greece. Every day more than 600,000 Romanian citizens take an antibiotic, an overuse with multiple and serious effects in time. We dedicate a good part of our budget of time to analyse this situation in our department, the only academic hospital for a 5 million population.

The results were published in the article: MULTIDROG RESISTANT URINARY TRACT INFECTIONS IN MOLDOVA, ROMANIA, FOCUSING ON UROPATHOGENES AND THEIR ANTIBIOTIC SUSCEPTIBILITY. CAN WE DO MORE? In Nobel Medicus 2015; 11(3) : 42-49.

The irresponsible overuse of antibiotics today, starting from different animal farms and continuing with the possibility to buy directly from the drug store without any medical document is the basic explanation for today’s situation: the rhythm in which the pharmaceutical industry can develop new molecules to help organisms fight infections is far less smaller that the possibility of the germs to become resistant.

In this way, there were recorded 2944 admissions, out of which 750 patients (25.47%) have developed urinary infections, while the number of MDR infections rose to 336, representing 11.41% of the total number of admissions and 44.80% of the total number of urinary infections. As regarding the periodicity manifested by the UTI MDR, we have noticed that these occur mainly in following months: March, April, May (spring) and June, July, August (summer) + more or less the September month (Table 14). A very important fact, is the prevailing germ that was present throughout the entire period was Klebsiella pneumoniae. Moreover, this had the same spectrum of resistance throughout the period: being resistant to ampicillin, amoxicilim + clavulanic acid, cephalosporins (cefuroxime, cefotaxime, ceftazidime, cefepime), gentamicin, fluoroquinolones (norfloxacin, ciprofloxacin).
Table 14. The periodicity of the cases during the 19 months of experiment.

<table>
<thead>
<tr>
<th>No.</th>
<th>Month</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>January 2013</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>February 2013</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>March 2013</td>
<td>33</td>
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<tr>
<td>4</td>
<td>April 2013</td>
<td>53</td>
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<tr>
<td>5</td>
<td>May 2013</td>
<td>19</td>
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<tr>
<td>6</td>
<td>June 2013</td>
<td>29</td>
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<td>7</td>
<td>July 2013</td>
<td>48</td>
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<td>8</td>
<td>August 2013</td>
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<td>9</td>
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</tbody>
</table>

Also, the second germ present for the duration of the experiment was Pseudomonas aeruginosa. In this case, the spectrum of resistance observed over the entire period included the following antibiotics: ceftazidime, cefepime, gentamicin and ciprofloxacin. This germ displayed high percentage resistance to the following antibiotics: cefoperazone - 75% (particularly during the summer and autumn months – May to November), meropenem - 66% (especially during the spring and summer, March to September), piperacillin - 50% (especially during the summer months June to September), imipenem - 50% (especially during the summer months June to September), levofloxacin - 50% (especially during the summer months June to September). In a lower percentage of resistance was also found to: cefotaxime - 25%, norfloxacin - 25%, tigecycline - 25%.

The third prevailing germ was *Escherichia coli*. It was present in > 66% (68%) of the investigation period. The spectrum of resistance observed during the course of the study included the following antibiotics: ampicillin, cephalosporins (cefuroxime, cefotaxime, ceftazidime), fluoroquinolones (ciprofloxacin, norfloxacin). High-percent resistance was identified for the following antibiotics: amoxicillin + ac. clavulanic 65% (especially in the
spring months of March to April and summer, June to August), cefepime - 50% (especially during the summer months- April - August). Additionally, in a smaller percentage it was resistant to gentamicin - 20%. Also, we have found high prevalence for other germs such as:

1. *Enterococcus faecalis/spp.* - present at a rate of ~ 75% (73.5%) during the period of study. The spectrum of resistance observed throughout the entire period included the following antibiotics: ampicillin, gentamicin, fluoroquinolones (levofloxacin, ciprofloxacin). A high percentage resistance was found for the following antibiotics: doxycycline - 85%, penicillin - 79% (especially in the spring months March to May and summer July to August).

2. *Staphylococcus coagulase-negative* - 75% / aureus 42% / saprophiticus 8.3%, present in 63% of the period of the study, for which we have found high-percent resistance to the following antibiotics: cefepim, imipenem, meropenem, penicillin, oxacillin - 83%, cefuroxime - 75%, fluoroquinolones (ciprofloxacin, levofloxacin) - 66% (especially during the spring and summer months, March to August), doxycycline - 50%, gentamicin, sulfamethoxazole - 42% (especially during the summer months - May - August). Also, a lower resistance percentage was found to clarithromycin - 16%.

Subsequently, we were particularly interested in finding whether long time urethral catheter represented a risk factor and the types of germs that would develop in those circumstances, especially since the patients had an increased risk of UTI MDR with most germs involved in their developing. In this way, analyzing the results from Table 2, the status of patient carrying an urethro-vesical catheter was UTI MDR associated with the following germs count:

- **Klebsiella pneumoniae/spp.** - in 46.15% of the UTI MDR cases with this germ;
- **Pseudomonas aeruginosa** - in 41.67% of the UTI MDR cases with this germ;
- **Escherichia coli** - in 38.10% of the UTI MDR cases with this germ;
- **Staphylococci** (S. coagulase-negative/S. aureus/S. saprophiticus) - in 57.14% of the UTI MDR cases with these germs;
- **Nonfermenting gram-negative bacilli** - in 28.57% of the UTI MDR cases with these germs;
- **Enterococcus faecalis/spp.** - in 40% of the UTI MDR cases with these germ;
- **Corynebacterium urealyticum** - in 50% of the UTI MDR cases with these germ;
- **Proteus vulgaris/mirabilis/spp.** – in 75% of the UTI MDR cases with these germ;
- **Enterobacter cloacae** – 66.67% of the UTI MDR cases with these germ.
Table 15. The relationship between long time uretro-vesical catheter and the type of germ.

<table>
<thead>
<tr>
<th>Germ</th>
<th>Urethral catheter (observed frequencies)</th>
<th>Total</th>
<th>Urethral catheter (theoretic frequencies)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Klebsiella pneumoniae/spp.</td>
<td>36</td>
<td>42</td>
<td>78</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>10</td>
<td>14</td>
<td>24</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>8</td>
<td>13</td>
<td>21</td>
</tr>
<tr>
<td>Staphylococcus coagulase-negative/S. aureus/S. saprophiticus</td>
<td>4</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Nonfermenting gram-negative bacilli</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Enterococcus faecalis/spp.</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Corynebacterium urealyticum</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Proteus vulgaris/mirabillis/spp.</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Citrobacter freundii/spp.</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
<td>87</td>
<td>156</td>
</tr>
</tbody>
</table>

To confirm the interdependence between these two factors (status of urethro-vesical catheter carrier and the type of germ), we used Pearson $\chi^2$ test (Pearson Chi-Square), as mentioned before. Thus, by using the data, we obtained a value of 49.39 for the $\chi^2$ statistical test. This value has to be confronted with the theoretical value of $\chi^2$, for a risk $\alpha$ of 0.05 and 10 degrees of freedom, for which we obtained $\chi^2_{0.05;10}=18.30$. Therefore, by comparing the calculated value of this test with the theoretical one ($\chi^2 = 49.39 > \chi^2_{0.05;10}=18.30$), we can conclude that there is a statistical significant association between the status of urethra-vesical catheter carrier and the type of germs.

Further on, in order to measure the level of association between our variables, the Cramer’s V coefficient was calculated. Based on our data, for this coefficient it was obtained a value of 0.5624, suggesting that between the factors represented by the bacteria type and status of urethro-vesical catheter there is a statistical significant dependence, with a high level of association. In addition, the most problematic germs were represented by:

- *Klebsiella pneumoniae/spp* - UTI MDR with *Klebsiella pneumoniae/spp.* was associated with the insertion and replacement of ‘JJ’ stents (33.33%), with endourological interventions (transurethral resection of the prostate - TUR-P 14.10%, transurethral resection of a bladder tumor - TUR-BT (23.08%), with clinical records of diabetes mellitus (19.23%), of bladder tumors (17.95%) or prostatic neoplasm (14.10%), with the status of urethro-vesical probe carrier (46.15%) and with the insertion of probes for percutaneous nephrostomy (15.38%).
- *Pseudomonas aeruginosa* - UTI MDR with *Pseudomonas aeruginosa* was associated with: the insertion and replacement of – JJ stents (58.33%), with endourological interventions (TUR-BT – 25%), with clinical records of bladder tumors (12.5%) and with the status of urethro-vesical probe carrier (41.67%).

- *Escherichia coli* - in this way, UTI MDR with *Escherichia coli* was associated with the insertion and replacement of – JJ stents (100%), with the insertion of probes for percutaneous nephrostomy (38.10%), with endourological interventions (uretheroscopy + UPGR - 14.29%), with history of urothelial tumors (19.05%) and with the status of urethro-vesical probe carrier (38.10%).

- *Staphylococci* (*coagulase-negative / S. Aureus / S. saprophiticus*) - UTI MDR with *staphylococci* was associated with: history of diabetes mellitus (28.57%), penian tumors (28.57%) and with the status of urethro-vesical probe carrier (57.14%).

- *Nonfermenting gram-negative bacilli* - UTI MDR with *nonfermenting gram-negative bacilli* was associated with the insertion and replacement of double J stents (57.14%), with endourological interventions (TUR-BT - 28.57%), with case history of bladder tumor (28.57%) and with the status of chronic urethro-vesical probe carrier (28.57%).

- *Enterococcus faecalis/spp.* - UTI MDR with *Enterococcus faecalis/spp.* was associated with: clinical records of diabetes mellitus (40%), bladder tumors (28.57%) and with the status of chronic urethro-vesical probe carrier (40%). On the other hand, the antibiotics that had almost no results regarding those infections were represented by:

  - Amoxicillin, ampicillin, amoxicillin + clavulanic acid, ampicillin + sulbactam;
  - Cephalosporins: ceftazidime, cefuroxime, cefotaxime, cefepime, cefoperazone, cefalexin, cefaclor, cefixime, cefitbuten, cefpirome, cefatarolone;
  - Gentamicin;
  - Fluoroquinolones: levofloxacin, ciprofloxacin, norfloxacin;
  - Penicillin, oxacillin;
  - Clarithromycin, erythromycin;
  - Doxycycline;
  - Sulfamethoxazole (as seen in Table 16).
Table 16. The results of the uroculture for the most used antibiotics

<table>
<thead>
<tr>
<th>ANTIBIOTIC</th>
<th>RESISTANT</th>
<th>SENSITIVE</th>
<th>INTERMEDIARY</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPICILLIN</td>
<td>346 (97.74)</td>
<td>8 (2.26)</td>
<td>0 (0)</td>
<td>354</td>
</tr>
<tr>
<td>AMOXICILLIN</td>
<td>2 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2</td>
</tr>
<tr>
<td>AMOXICILLIN + AC. CLAV.</td>
<td>275 (81.36)</td>
<td>33 (9.76)</td>
<td>30 (8.88)</td>
<td>338</td>
</tr>
<tr>
<td>AMPICILLIN SULBACTAM</td>
<td>+ 19 (86.36)</td>
<td>2 (9.09)</td>
<td>1 (44.55)</td>
<td>22</td>
</tr>
<tr>
<td>TICARCCILLIN</td>
<td>99 (25.78)</td>
<td>267 (69.53)</td>
<td>18 (4.69)</td>
<td>384</td>
</tr>
<tr>
<td>CEFTAZIDIME</td>
<td>412 (93.64)</td>
<td>27 (6.14)</td>
<td>1 (0.23)</td>
<td>440</td>
</tr>
<tr>
<td>CEFUROXIME</td>
<td>337 (98.54)</td>
<td>4 (1.17)</td>
<td>1 (0.29)</td>
<td>342</td>
</tr>
<tr>
<td>CEFOTAXIME</td>
<td>333 (95.68)</td>
<td>15 (4.31)</td>
<td>0 (0)</td>
<td>348</td>
</tr>
<tr>
<td>CEFEPINE</td>
<td>354 (80.45)</td>
<td>67 (15.23)</td>
<td>19 (4.32)</td>
<td>440</td>
</tr>
<tr>
<td>IMIPENEM</td>
<td>84 (23.26)</td>
<td>272 (75.35)</td>
<td>5 (1.39)</td>
<td>361</td>
</tr>
<tr>
<td>MEROPENEM</td>
<td>111 (26.3)</td>
<td>305 (72.27)</td>
<td>6 (1.43)</td>
<td>422</td>
</tr>
<tr>
<td>GENTAMICIN</td>
<td>326 (64.69)</td>
<td>162 (32.14)</td>
<td>16 (3.17)</td>
<td>504</td>
</tr>
<tr>
<td>NORFLOXACIN</td>
<td>313 (89.94)</td>
<td>27 (7.76)</td>
<td>8 (2.3)</td>
<td>348</td>
</tr>
<tr>
<td>CIPROFLOXACIN</td>
<td>397 (90.45)</td>
<td>34 (7.75)</td>
<td>8 (1.82)</td>
<td>439</td>
</tr>
<tr>
<td>CEFOPERAZONE</td>
<td>112 (81.74)</td>
<td>21 (15.33)</td>
<td>4 (2.92)</td>
<td>137</td>
</tr>
<tr>
<td>COLISTIN</td>
<td>11 (8.15)</td>
<td>121 (89.63)</td>
<td>3 (2.22)</td>
<td>135</td>
</tr>
<tr>
<td>TIGECYCLINE</td>
<td>33 (43.86)</td>
<td>40 (51.95)</td>
<td>4 (5.19)</td>
<td>77</td>
</tr>
<tr>
<td>ERTAPENEM</td>
<td>13 (17.34)</td>
<td>58 (77.33)</td>
<td>4 (5.33)</td>
<td>75</td>
</tr>
<tr>
<td>CEFALEXIN</td>
<td>3 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3</td>
</tr>
<tr>
<td>CEFACLOR</td>
<td>3 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3</td>
</tr>
<tr>
<td>CEFIXIME</td>
<td>16 (94.12)</td>
<td>1 (5.88)</td>
<td>0 (0)</td>
<td>17</td>
</tr>
<tr>
<td>CEFTIBUTEN</td>
<td>5 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>5</td>
</tr>
<tr>
<td>CEPFIPRONE</td>
<td>30 (78.95)</td>
<td>6 (15.79)</td>
<td>2 (5.26)</td>
<td>38</td>
</tr>
<tr>
<td>LEVOFLOXACIN</td>
<td>137 (93.20)</td>
<td>7 (4.76)</td>
<td>3 (2.04)</td>
<td>147</td>
</tr>
<tr>
<td>PENICILIN</td>
<td>52 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>52</td>
</tr>
<tr>
<td>OXACILIN</td>
<td>19 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>19</td>
</tr>
<tr>
<td>VANCOMICIN</td>
<td>2 (3.17)</td>
<td>61 (96.83)</td>
<td>0 (0)</td>
<td>63</td>
</tr>
<tr>
<td>CLARITROMICIN</td>
<td>4 (80)</td>
<td>1 (20)</td>
<td>0 (0)</td>
<td>5</td>
</tr>
<tr>
<td>ERITROMICIN</td>
<td>1 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>RIFAMPICIN</td>
<td>0 (0)</td>
<td>1 (100)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>LIONEZOLID</td>
<td>0 (0)</td>
<td>63 (100)</td>
<td>0 (0)</td>
<td>63</td>
</tr>
<tr>
<td>TEICOFLANIN</td>
<td>2 (3.13)</td>
<td>62 (96.87)</td>
<td>0 (0)</td>
<td>64</td>
</tr>
<tr>
<td>DOXYCYCLINE</td>
<td>48 (77.42)</td>
<td>13 (20.97)</td>
<td>1 (1.61)</td>
<td>62</td>
</tr>
<tr>
<td>SULFAMETOXAZOL</td>
<td>13 (68.42)</td>
<td>6 (31.58)</td>
<td>0 (0)</td>
<td>19</td>
</tr>
<tr>
<td>CEFTAZIDIME</td>
<td>1 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>FOSFOMICYN</td>
<td>2 (16.67)</td>
<td>9 (75)</td>
<td>1 (8.33)</td>
<td>12</td>
</tr>
</tbody>
</table>

Also, regarding Table 16 which included antibiotics and uroculture results, we decided to use a relative frequent statistical interpretation. According to these results we observe that the bacteria responsible for UTI development presented a 100% resistance to the following 9 antibiotics: amoxicillin (2 cases), ticarcillin (2 cases), cefalexin (3 cases), cefaclor (3 cases), cefitobuten (5 cases), penicillin (52 cases), oxacillin (19 cases), erythromycin (1 case) and ceftaroline (1 case). In addition, an increased resistance was also noticed for the following antibiotics: 98.54% for cefuroxime (337 out of 334 cases);
97.74% for ampicillin (346 out of 354 cases); 95.69% for cefotaxime (333 out of 348 cases); 94.12% for cefixime (16 out of 17 cases); 93.64% for ceftazidime (412 out of 440 cases), 93.20% for levofloxacin (313 out of 348 cases); 93.64% for ciprofloxacin (346 out of 354 cases); 93.64% for norfloxacin (137 out of 147 cases); 86.36% for ampiplus (19 out of 20 cases).

On the other side, UTI presents 0% resistance on the treatment with linezolid (0 out of 63 cases) and rifampicin (0 out of 1 case). Also, a very low resistance can be also observed in the treatment with: 13.3% for teicoplanin (2 out of 64 cases); 3.17% vancomycin (2 out of 63 cases) and 8.15% for colistin (11 out of 135 cases). We also managed to identify a so-called profile of the patient with UTI MDR, which would be represented by the following factors:

- Male: 71.57% of all cases during the period of study;
- Predominantly aged over 60, the peak incidence is between 60 and 80 years old;
- Diabetic - 16.88% of all cases during the period of study;
- With a history of neoplastic incidents - 43.51% cases during the study;
- Chronic beneficiary of urethral catheter or double J stent;
- With clinical records of transurethral resections (prostate, bladder tumors).

The presented data is highly relevant for the distribution and antibiotic susceptibility patterns of the bacterial species which were isolated in cultures from our UTI MDR patients. In this way, we have to mention even from the beginning that we consider our study very useful for the monitoring of the antibiotic susceptibility patterns at different uropathogens identified in Moldavia region, since this is extremely important not only because of the emerging problems in antibiotic resistance, but also in helping the aforementioned empirical therapy by developing a future antibiotic resistance database for prescriptions.

When it comes to the other results from literature, in first thing we have to mention is that other data is relevant up to a certain point, since the spectrum of resistance may vary in time, between different countries or regions it can also vary in the same country or even in different institutions.

Thus, while the findings of the aforementioned studies varied in some specific details, which we are not going to insist now, they all agreed that the main cause of this resistance could be either the self increased and unnecessary usage of antibiotics, the prescription of modern antibiotics with newer combinations in order to get a faster effect in different infections, continuous antibiotic pressure, lower dosage or shorter duration that may have resulted in a selection of mutant resistant strains.

In fact, in our study we reported that almost a quarter of the germs detected in UTI were MDR. As compared to the other studies described above, this is a very increased percentage. That is why we consider our study quite important, since it is, according to our best of knowledge, the first study in Romania testing these aspects in an important clinical center that is also representative for the entire Moldova area. These specific aspects for our country are very important considering the well-known problems regarding a somehow equivocal control on the drug prescription practices, and some problems as well with inadequate access to antibiotics (e.g. increased or misuse of them).

We do believe also that the increased prevalence of uropathogens described in
our present results is an important alarm signal. Even more, besides the connection between environmental parameters and UTI occurrences, in the present study we characterized, also for the first time in our country, a specific profile for the UTI-risk patient and, as we mentioned before, seems to be male, predominantly aged over 60, diabetic, with a history of neoplastic incidents, carrier of urethro-vesical catheter or JJ stent and also with clinical records of transurethral resections (prostate, bladder tumors).

This is of course very important, judging from the fact that a patient like that could be mentioned as a risky one, that needs to have his uroculture monitored and is also resistant or is responding to a specifically certain type of antibiotic. In addition, in accordance with international literature, we also noticed some seasonal modification in UTI manifestations that contribute furthermore to the already mentioned aspects.

Another related problem described in literature is represented by the recurrent UTI, since it was recently stated that a repeated course of antibiotics is often prescribed for the treatment and prevention of recurrent UTI, which could for example be used in resistant strains of uropathogenic Escherichia coli.

Unfortunately we are facing the situation in which patients depending on chronic urethral catheters are receiving - unjustifiably! - antibiotic medication for an illusory prevention of the infection. This still widespread attitude in our medical world (as it is not only the urologist that regularly changes the catheter!) does not bring any benefit to the patient, because the urinary infection - asymptomatic bacteriuria - will develop anyway, and in addition it will also decisively help the pathogens acquire antibiotic resistance, which will lead to complications if possible antibiotherapy is necessary at some point. In this way, the latest EAU guides clearly recommends that only the infectious complications that occur in the patients with urethral catheters should be strictly targeted and treated, based on the antibiogram.

We do believe that one possible solution that could be considered is represented by stopping the administration of some classical drugs such as the norfloxacin, ciprofloxacin or levofloxacin for an amount of time. This could perhaps result in a reactivation of the sensitivity for the germs, of course after these drugs are hypothetically not prescribed in the hospital or at home for a fair amount of time, like the possible case of nitrofurantoin. In fact, if we look at the previous literature for the nitrofurantoin, it was found to be active against most of uropathogens and to have a low resistance and in this way it remains an important option that should be considered for the treatment of UTI.

One possible explanation for this will be represented by the fact that nitrofurantoin is not closely related to other antimicrobials and therefore cross-resistance is unlikely to develop, as well as the aforementioned fact that we could talk about a possible reactivation of the germs sensitivity after a time of non-administration.

Suggestively, nitrofurantoin, a drug involuntarily abandoned when the promising new 2nd and 3rd generations of quinolones were introduced, is often the only efficient weapon with oral administration to which the multidrug resistant germs, especially the E. coli, are exhibiting sensitivity, according to the antibiogram.

Moreover, antibiotics must be also used with prudence to treat recurrent UTI effectively. Also, in regards to the morbidity and treatment costs, the MDR urinary
tract infections are a very important problem of public health. Therefore, treatment should be done in accordance with the antibiogram results and for a sufficient period of time, in order to avoid the appearance of pan-resistant germs for which there are no reserve antibiotics available. Additionally, discarding certain commonly used antibiotics, to which the great majority of the strains are resistant, for a period of time, could perhaps lead to a possible shift in the spectrum of their sensitivity. In this way, considering all the aforementioned features, it seems that some regional surveillance studies, like we did in our present study are more than welcomed.

In the present report we were interested to determine the community associated UTI uropathogen's prevalence, the antibiotic resistance patterns and the risk factors associated with it in the most important clinical facility of this type in Moldova region, Romania. Our data showed that mainly the most problematic germs were represented by *Klebsiella pneumoniae/spp.*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Staphylococci (coagulase-negative/ S. aureus/ S. saprophiticus)*. Also, the bacteria responsible for UTI MDR development presented a 100% resistance to the following nine antibiotics: amoxicillin, ticarcillin, cefalexin, cefaclor, cefitibuten, penicillin, oxacillin, erythromycin and ceftaroline. Moreover, an increased resistance was also observed for the following antibiotics, in the following order: cefuroxime, ampicillin, cefotaxime, cefixime, ceftazidime, levofloxacin, ciprofloxacin, norfloxacin and ampicillin + sulbactam.

In addition, for the first time in our country, a specific profile for the UTI MDR-risk patient was described in the present paper, being represented by male gender, predominantly aged over 60, diabetic, with a history of neoplastic incidents, carrier of urethro-vesical catheter or double J stent and also with clinical records of transurethral resections (prostate, bladder tumors).
II.4. METABOLIC SYNDROME

II.4.1 SMALL LDL AND THE METABOLIC SYNDROME

Urologic patients may have, among the kidney / bladder / prostate pathology also a metabolic syndrome, with specific consequences upon the general health level and on the recurrence of the urologic pathologies (for example lithiasic pathology). Studying the problem together with our colleagues from the University’s Biochemistry Department we have dedicated two projects to this subject. The day by day practice shows that the connections between lithiasis and metabolic syndrome are visible and important:

- on one hand, the metabolic syndrome can explain for various reasons the relapse of the lithiasic episodes;
- on the other hand the obese patients are harder to treat, despite new methods and technologies.

The first article is: SMALL LDL: A HELPFUL PARTICLE IN MONITORING PATIENTS WITH METABOLIC SYNDROME, published in Farmacia journal in 2016.

The study was conducted between 01.04.2014 and 01.03.2015 on 102 patients (72 males and 30 females) with metabolic syndrome, diagnosed according to National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP III) criteria. The patients that were included in the study presented changes only for the lipid parameters values, the glycemia levels being in the normal range. The test panel included biochemical markers of lipid profile: triglycerides (TG), total cholesterol, HDL-cholesterol, LDL-cholesterol, sLDL. Blood samples were collected; serum was separated after blood centrifugation at 4000 g for 15 minutes. Triglycerides and total cholesterol concentrations were assessed using spectrophotometric enzymatic methods. HDL-cholesterol was assessed after the precipitation of chylomicrons, VLDL (very low density lipoproteins) and LDL with phosphotungstic acid and MgCl2, followed by determination of HDL- cholesterol in the supernatant. LDL-cholesterol concentration was measured using a direct colorimetric enzymatic method, which implied micellar solubilisation of LDL-cholesterol by a non-ionic detergent and interaction between lipoproteins (VLDL and chylomicrons) and a polysaccharide compound. The method fulfils the NCEP (National Cholesterol Education Program) requirement of total analytical error ≤ 12% [10]. sLDL fraction concentration was measured using a “two step” method, with surfactant and specific enzymes. The determinations were performed on a RX-Imola automatic analyser, using RANOIX kits with calibrators and control sera included. The carotid ultrasound examination was performed by a sonographer, using an ESAOTE MyLab50 with 2.5/3.5 MHz probe.
The quantification of the atherosclerotic process was made measuring the ejection fraction (LVEF), of the left ventricle mass (LVM) and aortic atheroma. Statistical analyses were performed using SPSS / v. 20, (t-Student test, Mann-Whitney U test).

The descriptive statistics bring the following results: out of the 102 analysed patients, 72 (70.58%) were male, 30 (29.41%) were female and the mean age was 49.10 ± 12.45 years. The average values along with standard deviation for age, lipid profile (cholesterol, LDL, sLDL, HDL, TG, LDL/HDL ratio) and cardiac function parameters (left ventricular ejection fraction - LVEF and left ventricular mass - LVM) by sex are shown in Table 17. The variation of lipid parameters is depicted in Figure 1. The evaluation of the lipid parameters was performed in relation to the reference ranges for the age groups that were included in the study.

![Figure 1. The variation of the lipidic profile](image)

**Table 17. Mean values of the studied parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Men (mean ± standard deviation)</th>
<th>Women (mean ± standard deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.056 ± 15.615</td>
<td>52.115 ± 11.582</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>248.842 ± 67.894</td>
<td>251.963 ± 54.665</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>50.505 ± 7.759</td>
<td>45.367 ± 12.896</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>165.789 ± 55.090</td>
<td>156.913 ± 51.197</td>
</tr>
<tr>
<td>sLDL (mg/dL)</td>
<td>61.558 ± 26.805</td>
<td>65.856 ± 28.612</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>344.210 ± 239.970</td>
<td>426.993 ± 254.041</td>
</tr>
<tr>
<td>LDL/HDL ratio</td>
<td>3.239 ± 0.861</td>
<td>3.581 ± 1.192</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>65.500 ± 6.833</td>
<td>60.230 ± 10.497</td>
</tr>
<tr>
<td>LVM (g)</td>
<td>216.333 ± 57.109</td>
<td>271.760 ± 80.684</td>
</tr>
</tbody>
</table>

The statistical analysis by Student t-test did not show significant statistical differences between the up-mentioned parameters by sex groups, while a positive Pearson correlation was obtained by comparing male and female gender. The statistical analysis revealed that 68.4% of the patients presented left ventricular dysfunction assessed by cardiac echocardiography while the majority of subjects (94.7%) had aortic atheromatosis.
The total cholesterol values had positive and significant correlations with HDL, LDL and sLDL, while LDL correlated with HDL, sLDL, respectively. HDL/LDL ratio. The triglycerides levels presented positive associations with the left ventricular ejection fraction and high sLDL values. The following correlations have been obtained: HDL - cholesterol \( r = 0.587, p = 0.008 \), LDL - cholesterol \( r = 0.782, p < 0.001 \), sLDL - cholesterol \( r = 0.845, p < 0.001 \), LDL-HDL \( r = 0.512, p = 0.025 \), LDL-sLDL \( r = 0.711, p = 0.001 \), LDL - HDL/LDL ratio \( r = 0.480, p = 0.038 \), sLDL-triglycerides \( r = 0.28, p = 0.01 \), triglycerides - left ventricular ejection fraction \( r = 0.490, p = 0.033 \). T-test statistical differences have been significant \( p < 0.001 \), considering sLDL values compared to LDL, cholesterol and triglycerides.

Our results show that sLDL could be a valuable marker for the risk of coronary heart disease, better than the LDL levels, in patients with metabolic syndrome. The value of this marker is increased and statistically correlated with age and triglycerides levels. sLDL can bring its contribution not only in the evaluation of atherosclerosis risks, but also in monitoring individual therapies.
II.4.2 *ASN291SER* IN CARDIOMETABOLIC SYNDROME

Another study was about THE PREVALENCE OF *ASN291SER* MUTATION IN THE LIPOPROTEIN LIPASE GENE IN A POPULATION WITH CARDIOMETABOLIC SYNDROME FROM NORTH EAST ROMANIA, published in Revista de Chimie on March, 2016. The clinicians came along with biochemistry and genetic specialists in order to evaluate better the cardiometabolic syndrome.

We evaluated 76 patients (55 males and 21 females) with cardiometabolic syndrome presenting abnormal values of the lipid parameters, the mean age being 49.10 ± 12.45 years. The patients originated from North East Romania. The NCEP III (National Cholesterol Education Program) criteria for cardiometabolic syndrome are: abdominal obesity characterized by waist circumference > 102 cm for males and > 88 cm for females, fasting glycemia > 110 mg/dL or confirmed diabetes mellitus, serum triglycerides ≥ 150 mg/dL, HDL cholesterol < 40 mL/dL in males and < 50 mg/dL in females, arterial blood pressure ≥ 135/80 mmHg (Expert Panel on Detection). To ascertain the diagnosis of cardiometabolic syndrome, three of the five criteria must be met.

In our study we selected the patients that met the following three criteria: abdominal obesity, changes of at least one of the lipid parameters and changes of the arterial blood pressure. We choose to select patients in this way, focusing on the changes of the lipid profile, based on the fact that in the scientific literature dyslipidemia in the cardiometabolic syndrome is considered to be one of the most important risk factors in the pathogenesis of atherosclerosis. For the selected patients we searched for the presence of *Asn291Ser* mutation in the LPL gene and we determined the levels of lipid profile parameters.

The values of the main lipid parameters were determined in serum samples, after an overnight fast. Triglyceride measurement was performed by a spectrophotometric assay using specific enzymes (Fossati and Principe method), coupled with the Trinder’s reaction. Total cholesterol was measured using an enzymatic spectrophotometric assay. For the determination of cholesterol fractions specific reagents were used and the following steps were followed.

(a) HDL cholesterol: precipitation of chylomicrons, VLDL and LDL particles with phosphotungstic acid and MgCl₂, followed by centrifugation and measurement of HDL cholesterol in the supernatant.

(b) LDL cholesterol: a direct enzymatic chlorimetric method was used. This is based on the selective micellar solubilization of LDL cholesterol with a non-ionic detergent coupled to the use of a carbohydrate compound that interacts with VLDL and chylomicrons and prevents the reaction of cholesterol present in these particles with the reagents used in the assay. This allows the selective measurement of LDL cholesterol in serum. This method meets the NCEP (National Cholesterol Education Program) requirements of having a total analytical error ≤ 12%.

The serum concentration of small dense LDL particles (sLDL) was also determined, taking into account the atherogenic role of this lipoprotein fraction. A „two step‖ technique was performed using surfactant and specific enzymes. The assays described above were performed on a compact analyzer of wet chemistry of RX-Imola type.

In this study we searched for the presence of the LPL *Asn291Ser* mutation in the 76 patients with cardio-metabolic syndrome. To detect this mutation we used a mismatch PCR
primer as the 3’-PCR primer together with the normal 5’-PCR primer. DNA amplification of exon 6 with the two primers generates a 238-bp fragment. The Asn291Ser substitution in the LPL protein is caused by an A to G mutation located at nucleotide 1127 in exon 6 of the LPL gene. The use of a mismatch primer generates a C instead of the normal A (the mismatch) at nucleotide 1130 in the PCR fragments amplified from both the mutant and normal alleles. Thus, in the PCR fragment from the mutant allele, a recognition site for the Rsa I restriction endonuclease will be created: 5’-GTAC-3’ (G112 from the Asn291Ser mutation and C1130 from the mismatch). As a consequence, this 238-bp fragment will be cleaved into a 215-bp fragment and a 23-bp fragment. The PCR product from the normal allele will have a 52-ATAC-32 sequence in this region and cannot be cleaved by the Rsa I enzyme, therefore remaining as a single 238-bp fragment.

In our study, the Asn291Ser mutation in the LPL gene was found with a carrier frequency of 2.63% among the 76 patients with cardiometabolic syndrome. This frequency is lower compared to that reported by other studies. The Asn291Ser mutation has been found with a carrier frequency of 5.2% in a group of 807 Dutch patients with CHD, 4.5% in a group of 899 men from the United States with CHD and low HDL cholesterol levels, and 3.3% in a group of 721 Australian subjects with CHD. We consider that this difference in the carrier frequency between our study and other reports might be explained by the fact that our group was significantly smaller compared with the others. In this study we also aimed to analyse the presence of the Asn291Ser mutation in correlation with the serum levels of triglycerides, HDL cholesterol and small dense LDL.

We found that the female carrier subject of our study had a serum TG level increased by 9.8% and an HDL cholesterol level decreased by 5.41 mg/dL compared with the corresponding mean values of the female subgroup. These results are in accordance with those reported by several studies. A meta-analysis performed by Hu et al. on 21 studies published up to 2004 and including ~19 000 subjects revealed that the Asn291Ser variant in the LPL gene was a risk factor for dyslipidemia, characterized by hypertriglyceridemia and low HDL cholesterol levels. Based on the evaluation of 19 studies published up to 2007 and including ~24 000 participants.

Our study shows that one of the most common LPL mutations, Asn291Ser, may be a factor in the development of atherogenic dyslipidemia associated with cardio-metabolic syndrome, characterized by hypertriglyceridemia, low HDL cholesterol levels and increased sLDL levels. We consider that the identification of such a genetic factor, that increases the cardiovascular risk, will help the patient, as well as his physician, to focus on decreasing or eliminating the modifiable risk factors (such as smoking or obesity), thus favoring therapeutic efficiency. We are aware of the limitations of this study in relation to the number of patients that were investigated. Nevertheless, the finding of two carriers among 76 subjects with cardiometabolic syndrome imposes the continuation of the research on a larger group of patients, as well as its extension in the general population. At the same time, we consider that the investigation of the first degree relatives of the two carriers would be appropriate, in order to prevent the early onset of cardiovascular disease, thus contributing to the improvement of life quality.
II.5. PROSTATE CANCER

Prostate cancer is the most common solid cancer in Europe as well as in USA and it is now considered one of the most important healthcare problems. It has an incidence of 214 cases per 100000 men in Europe. The lifetime risk of disease is about 40% for incidental finding of the disease (during autopsy) and about 9.5% for clinically significant prostate cancer. The lifetime risk of death in men from prostate cancer is about 3%, which represents the second greatest cause of male cancer mortality. Approximately 50% of the risk of developing this cancer is attributed to genetics and 50% to environmental factors.

**Age**

The risk of prostate cancer increases with age. Autopsy studies report an incidence of 30% prostate cancer among male older than 50 years, 40% between 60 and 79 years and climbs to about 70% by the eight decade of life. However, the vast majority of prostate cancers do not become clinically significant.

**Race and geographical variation**

There is a strong geographical effect on the incidence of prostate cancer. This can be attributed to both race and environmental factors. Men from the Far East have the lowest incidence of prostate cancer in the world, although migration studies show that this risk increases if they move to the West. In USA African Americans have a higher incidence (1.6X) of prostate cancer compared with white men and the incidence in other ethnic groups is lower.

Interestingly, even if the clinical incidence of prostate cancer has wide variations, the frequency of the disease detected during autopsy is roughly the same in different parts of the world.

**Family history**

About 9% of patients have true hereditary disease defined as:

a) three or more relatives with prostate cancer;

b) at least two relatives diagnosed with prostate cancer before 55 years.

Thus, the risk is at least doubled if there is one first-degree relative affected by the disease and it climbs to 5-11-fold if there are two or more relatives affected.

**Dietary factors**

Dietary factors that may prevent the disease are: vitamin C, E and D, carotenoids, the anti-oxidant lycopene (cooked or processed tomatoes), fruit and vegetable intake, minerals (calcium, selenium) and phyto-oestrogens (flavonoids, ligands, isoflavonoids). Disease prevention strategies also recommend a lower intake of animal fat as part of the lifestyle changes, especially for the male relatives of prostate cancer patients.

**PATHOLOGY**

The most common prostatic malignancy (>95%) is adenocarcinoma. Transitional cell carcinoma represents 4.5% of other histological diagnoses, and neuroendocrine carcinomas, sarcomas, hematologic malignancies and metastases (malignant melanoma, colorectal
carcinoma, pulmonary) about 0.5%.

Adenocarcinomas arise from the acinar or ductal epithelium. It is a multifocal disease in 85% of cases. The majority of prostate cancer is located in the peripheral zone: 75%. From the transition zone originate 20% and from the central zone about 5%.

The tumour is referred to as confined when completely contained within the prostate and locally advanced when there is local extension into the extraprostatic tissue. Extension occurs preferentially to the posterior and posterolateral parts of the prostate and it is facilitated by the lack of a histologic prostatic capsule. Adenocarcinomas also tend to spread along the nerves – perineural invasion. Locally the tumour may invade the seminal vesicles, urethral sphincter, bladder and ureters, but rarely rectum, which is protected by Denonvillier’s fascia. The most common sites of metastasis are internal iliac lymph nodes and bones followed by lungs, liver and adrenal glands.

Tumour staging uses the 2009 TNM (Tumour, Node, Metastasis) classification:

**T primary tumour**
- TX - Primary tumour cannot be assessed;
- T0 – No evidence of primary tumour;
- T1 - Clinically inapparent tumour not palpable or visible by imaging;
- T1a - Tumour incidental histological finding in 5% or less of tissue resected;
- T1b - Tumour incidental histological finding in more than 5% of tissue resected;
- T1c - Tumour identified by needle biopsy (e.g. elevated prostate, >PSA level);
- T2 - Tumour confined within the prostate;
- T2a - Tumour involves one half of one lobe or less;
- T2b – Tumour involves more than half of one lobe, but not both lobes;
- T2c – Tumour involves both lobes;
- T3 - Tumour extends through the prostatic capsule;
- T3a - Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement;
- T3b - Tumour invades seminal vesicle(s);
- T4 - Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall.

**N Regional lymph nodes clinical**
- NX - Regional lymph nodes cannot be assessed;
- N0 - No regional lymph node metastasis;
- N1 - Regional lymph node metastasis.

**M Distant metastasis**
- M0 - No distant metastasis;
- M1 - Distant metastasis;
- M1a - Non-regional lymph node(s);
- M1b - Bone(s);
- M1c - Other site(s).

T1c - Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c.
Microscopically adenocarcinoma of the prostate is graded 1-5 according to its glandular differentiation, with 1 being the most differentiated. The Gleason score is the sum of the two most common grades seen on a biopsy core or an operative specimen. It has a value between 2 and 10 with 10 being the most aggressive. The Gleason score is a good predictor of prognosis.

**DIAGNOSIS**

*Clinical presentation*

Since most prostate cancers arise in the peripheral zone, most patients with early-stage disease are asymptomatic. Diagnosis is suggested by a raised PSA and/or an abnormal digital rectal examination. At an early stage, the patient might have lower urinary tract symptoms because of a co-existing pathology (benign prostatic hyperplasia, prostatitis); these symptoms may include poor bladder emptying, urinary retention, overactive bladder, haematuria, haemospermia or perineal discomfort. In locally advanced cancer, obstructive and/or irritative complaints can be caused by the tumour growth into the urethra or bladder neck and are similar to the above. Renal failure can occur either due to urinary retention or direct extension of cancer into the trigone of the bladder, followed by ureteric obstruction. Lymphatic obstruction may cause swelling of the legs or genitalia. Metastatic disease to the bones may cause pain, anaemia, pathological fracture, or symptoms of cord compression. Cord compression is a particularly important complication to detect and treat early. It is characterised by progressive paresthesia and weakness of the lower extremities with urinary faecal incontinence all of which can be permanent if not treated quickly. Hepatic and lung metastasis may cause pain, jaundice and dyspnoea.

*Digital rectal examination (DRE)*

Digital rectal examination is a classic component of the physical examination but it lacks specificity and sensitivity. A normal DRE does not exclude prostate cancer. A palpable irregularity has about 50% probability of being a carcinoma, but any suspect DRE is an absolute indication for prostate biopsy (even with a PSA below 2 ng/ml the probability of finding cancer is up to 30%). Most prostate cancers arise in the peripheral zone of the prostate and may be detected by DRE when the volume is above 0.2 mL. The findings depend on the clinical stage of the disease:

- **T1:** no changes at DRE;
- **T2:** a single or multiple, firm, hard, nontender nodule or an induration or asymmetry of the prostatic gland;
- **T3, T4:** the whole prostate is big, hard and irregular.

Prostate-Specific Antigen (PSA) is an organ specific kallikrein-like serine protease produced by the epithelial cells of the prostate. PSA serum levels may be elevated in the presence of prostate cancer but also of non-malignant conditions like: benign prostatic hypertrophy, acute or chronic prostatitis, lower urinary tract instrumentation, urinary retention and bladder catheterisation. Minor elevations have been described after ejaculation and DRE. PSA serum level is a continuous parameter: the higher the value the more likely is a diagnosis of prostate cancer.
For a PSA level:

- between 3.1 - 4 ng/mL the risk of prostate cancer is 26.9%;
- between 4 - 10 ng/mL the risk is 25% (normal DRE) or 45% (abnormal DRE);
- above 10 ng/mL the risk of prostate cancer is about 50-80%.

Modifications of serum PSA value have been described in order to improve its specificity:

- Free/total PSA ratio: may be used to discriminate benign hypertrophy from cancer of the prostate in patients with PSA value between 4 and 10 ng/mL and normal DRE. A value below 0.10 suggests prostate cancer.
- Complexed PSA is an alternative fraction of PSA that is reported to have a higher accuracy for detecting prostate cancer than PSA alone.
- PSA velocity: absolute increase in serum PSA (ng/ml/year). A rise of greater than 0.75 ng/ml/year or 20% per year, in PSA range 4-10 ng/ml, should prompt the recommendation of a biopsy.
- PSA doubling time: the time it takes for the PSA to double. A doubling time < 5 years should rise suspicion of the presence of prostate cancer.

**PCA3 marker**

PCA3 is a molecular marker measured in urine sediment after prostatic massage. It is reported to have a higher sensitivity and specificity for prostate cancer than PSA.

**Transrectal ultrasonography (TRUS)**

Greyscale ultrasound of the prostate using an endorectal probe is a standard imaging investigation of the prostate. If the prostate cancer is visible, it appears as a hypoechoic area in the peripheral zone of the prostate. However most prostate cancers are iso-echoic and it can also appear hyper-echoic during ultrasound. Thus, the reliability of greyscale TRUS for detecting prostate cancer is not adequate, although it is useful for guiding biopsy and can be useful for staging of cancer. Colour Doppler, microbubble imaging and tissue elastography have been used to enhance the accuracy of TRUS in the detection of prostate cancer with transrectal or perineal approach and it is used for prostate biopsies depending on urologist preference. The traditional sextant protocol is no longer the standard. At least eight cores should be sampled.

**STAGING**

Many patients with newly diagnosed prostate cancer do not require staging because the risk of metastasis can be as reliably predicted by nomograms as it can be by currently available investigations. Indeed, only those identified by nomograms as high risk of advanced or metastatic disease are typically staged before considering treatment options. MRI is the staging investigation of choice, even though accuracy for both local and nodal staging is variable. The accuracy of MRI can be improved by the use of an endo-rectal coil and multiparametric imaging, which includes diffusion weighting and spectroscopic techniques. Computed tomography has a low sensitivity to evaluate the local extent of the disease and is
not routinely recommended. Like MRI, it may be useful in investigating those at risk of nodal
disease, when a threshold of 1 cm in the short axis for oval nodes, and 0.8cm for the round
nodes, are considered criteria for the diagnosis of lymph nodes metastases.

The gold standard for N-staging is lymphadenectomy (open or
laparoscopic).

Prostate cancer metastasizes most commonly to the bones. Elevated alkaline
phosphatase levels may indicate the presence of bony metastasis in 70% of cases.

Bone scintigraphy is the most sensitive method to detect bone metastasis. It is
indicated for the investigation of newly diagnosed patients with a PSA>20ng/mL, clinical
reasons, or major component of histological grading 4 or 5 in the biopsies.

If symptoms suggest the possibility of soft-tissue metastasis, ultrasound, chest X-ray,
CT and MRI (marrow screening) may all be appropriate to investigate the patient.

DIFFERENTIAL DIAGNOSIS

Abnormal DRE is also found in: prostatic calculi, post-TURP or prostate biopsy,
chronic granulomatous prostatitis. Different causes that elevate serum PSA (see above) have
to be considered when evaluating the patient. Lower urinary tract symptoms described in
locally advanced disease are also found in: benign hyperplasia of the prostate, bladder calculi,
prostatitis and urethral strictures. Paget’s disease may mimic prostatic bone metastases
causing an elevated alkaline phosphatase and sclerotic bone lesions on plain x-ray films. However, the PSA and the DRE of the patient are normal.

TREATMENT

The management of patients with prostate cancer is complex and it is essential to
discuss it and its implications, with the patient, as well as anyone else he wishes to involve.

Deferred treatment

Watchful waiting defines conservative management of cancer until local or systemic
progression, when palliative treatment for urinary obstruction (TUR-P) and hormonal
therapy and/or radiotherapy is started. It is an option for patients with a limited life
expectancy, based on the observation that prostate cancer is a slowly progressive disease. The
disease specific survival at 10, 15 and 20 years is about 85%, 75% and respectively 40%
without treatment.

Active surveillance defines the active decision not to treat the patient immediately and
to follow him with close surveillance. It was a treatment strategy recently introduced because
PSA screening has led to the detection of an increasing number of patients with low-risk
cancers, and addresses the concern that many of these patients may not need or benefit from
radical treatment.

Deferred treatment is an option in:

- Stage T1b-T2b with well and moderately differentiated tumours, asymptomatic
  patients with a life expectancy of < 10 years;
- Stage T1a: younger patients with a life expectancy of < 10 years with well and
  moderately differentiated tumours need re-evaluation with PSA, TRUS and biopsies of the
prostatic remnant;
- Stage T1c-T2a in patients with PSA ≤ 10, Gleason ≤ 6, ≤ 2 positive biopsies, ≤ 50% cancer per biopsy – inclusion criteria for active surveillance.
- Stage T3-T4 with well and moderately differentiated cancer and short life expectancy especially if PSA < 50 and PSA doubling time < 12 months.

**Radical prostatectomy**

Radical prostatectomy involves complete removal of the prostate gland and seminal vesicles and usually includes a modified pelvic lymph node dissection as well. The best way to cure cancer in a localized disease is the total surgical removal. Surgical approaches to radical prostatectomy are: perineal, retropubic, laparoscopic (through a transperitoneal or extraperitoneal approach) and robotic.

Hugh Hampton Young was the first to perform a radical perineal prostatectomy in 1904. The first radical retropubic prostatectomy was described by Millin in 1945. Improved understanding of the periprostatic anatomy, introduced by Patrick Walsh in the 1980s, resulted in a significant reduction in blood loss and improved continence and potency rates. Formal nerve sparing radical prostatectomy is an option in pre-operatively potent patients with low risk of extracapsular disease in order to improve the potency rates.

Radical prostatectomy is the only treatment for localized prostate cancer with proved benefit for cancer specific survival compared with conservative management.

It is indicated for the treatment of fit men with a life expectancy ≥ 10 years with low and intermediate risk localised prostate cancer (T1a-T2b and Gleason score 2-7 and PSA ≤ 20). It may represent an option for:
- the patients with stage T1a and a life expectancy ≥ 15 years or Gleason score 7;
- selected patients with low volume high-risk prostate cancer (T3a or Gleason 8-10 or PSA<20);
- selected patients with very high risk disease (T3b-T4 N0 or any T N1) as a part of a multimodal treatment.

Morbidity associated with radical prostatectomy is significant and is related to the experience of the surgeon. Peri-operative death varies between 0.0 and 2.1%.

**General complications of any major surgery:** bleeding (1.0-11.5%) requiring transfusion and/or re-operation, infection requiring antibiotics, deep vein thrombosis (0.0-8.3%), pulmonary embolism (0.8-7.7%).

**Early postoperative complications:** urine leak (0.3-15.4%), lymphocele (1.0-3.0%), rectal, ureteral or obturator nerve injury, should be corrected as soon as recognized.

**Late postoperative complications include:**
- erectile dysfunction (29.0-100%) - nerve sparing techniques improve outcomes;
- incontinence: slight stress incontinence (4.0-50%) or severe stress incontinence (0.0-15.4%) is due to injury of the external urethral sphincter complex - pelvic floor exercises, peri-urethral bulking injections, and implantation of an artificial urinary sphincter may be necessary to manage this complication.
- bladder neck stenosis (0.5-14.6%) – which is treated by endoscopic bladder neck incision.
Radiation therapy

Radiation treatment can be administered as either external beam radiotherapy or interstitial brachytherapy. These techniques can be used in isolation or combined to boost the radiation dose to the prostate. Its efficacy is improved by months of neo-adjuvant androgen ablation treatment, which may be continued for several years after the radiotherapy in higher risk cases. Three-dimensional conformal radiotherapy is the current gold standard for the administration of external beam radiotherapy, with the more precise technique of intensity modulated radiotherapy gradually gaining ground. Transperineal brachytherapy is safe and effective.

Radiation therapy is recommended in:
- stage T1c/T2cN0M0 even for young patients who refuse surgical intervention;
- immediate post-operative (adjuvant) external irradiation after radical prostatectomy for patients with pathological stage T3N0M0;
- delayed post-operative (salvage) external irradiation after radical prostatectomy for patients with a rising PSA;
- locally advanced prostate cancer T3-4N0M0 associated with concomitant and adjuvant hormonal therapy;
- stage T1-T2a, Gleason score < 7, PSA ≤ 10, prostate volume ≤ 50mL in combination with transperineal interstitial brachytherapy.

Contraindications for external beam radiotherapy:
- severe lower urinary tract symptoms;
- inflammatory bowel disease;
- previous pelvic radiation.

Complications for external beam radiotherapy are lower urinary tract symptoms, haematuria (4.7%), gastro-intestinal symptoms (16%), urinary stricture (7.1%), urinary incontinence (5.3%), erectile dysfunction (30-50%) and the risk of a second solid pelvic malignancy.

Contraindications for transperineal brachytherapy:
- previous TURP + Prostate volume<50ml;
- moderate to severe lower urinary tract symptoms.

Complications of transperineal brachytherapy include: perineal haematoma, lower urinary tract symptoms including urinary retention, urinary incontinence (5%) and erectile dysfunction (50%).

Hormonal therapy (Androgen ablation therapy)

Hormonal therapy has become the mainstay of management for advanced prostate cancer since Huggins and Hodges proved the responsiveness of prostate cancer to castration.

Androgen deprivation can be achieved by:
- Suppressing the secretion of testicular androgens: surgical castration (bilateral orchietomy), LHRH agonists (busereline, gosereline, leuproleline and triptoreline),
oestrogens (diethylstilbestrol), LHRH antagonists (abarelix, degarelix).

- Inhibiting the action of circulating androgens at the level of their receptor: steroidal anti-androgens (cyproterone acetate, megestrol acetate and medroxyprogesterone acetate) and non-steroidal anti-androgens (bicalutamide, flutamide and nilutamide).

Indication for castration:
- stage M1 either symptomatic (to palliate symptoms and reduce the risk of potentially fatal complications) or asymptomatic (to defer progress to symptomatic stage);
- stage N+ (prolong overall survival);
- locally advanced disease, especially if there are local symptoms to palliate, such as bladder outflow obstruction;
- side-effects include: loss of libido, erectile dysfunction, hot flashes, bone problems, obesity and sarcopenia, lipid alteration and insulin resistance, metabolic syndrome, diabetes and cardiovascular disease.

**Complete androgen blockade**

Castration reduces serum testosterone levels by up to 95% but, an intraprostatic stimulus is maintained by the androgens of adrenal origin. 

Complete androgen blockade is obtained by either surgical or pharmacological castration.

Castration refractory prostate cancer defines the prostate cancer that relapse after initial androgen ablation therapy. This form of cancer responds to secondary hormonal manipulations (such as: anti-androgen withdrawal, oestrogens and corticosteroids) and is different from hormone resistant prostate cancer which is resistant to all hormonal measures. For metastatic hormone resistant prostate cancer there are several chemotherapeutic options, docetaxel being the most studied. All patients who receive docetaxel will progress in six to eight months. Cabazitaxel and Abiraterone are regarded as first choice options for salvage chemotherapy.

Bevacizumab (a monoclonal antibody), aflibercept (VEGF trap), sunitinib (anti-VEGFR), dasatinib (anti-Src), suramin and vaccines are being tested for hormone resistant prostate cancer.

Castration refractory and resistant prostate cancer are treated with supportive care, which involves a number of different forms of palliative management:
- Those that are directed at quality of life improvement and pain reduction;
- Radionuclides, external beam radiotherapy and analgesics to control painful osseous metastases;
- Transurethral resection of the prostate in order to treat complete urinary retention;
- Percutaneous nephrostomy to palliate renal failure;
- Bisphosphonates can be proposed to patients with hormone resistant prostate cancer and bone metastases, in order to prevent osseous complications. Patients should have a dental examination prior to starting the treatment, because of the risk of jaw necrosis.
- Spinal surgery and decompressive radiotherapy are emergency procedures for patients with neurological symptoms caused by spinal cord compression.
No clear-cut recommendation can be made for the most effective drug for secondary hormonal manifestation. Drugs like abiraterone and MDV3100 are still in study.

**Follow-up**

Follow-up should be tailored for the individual patient, according to symptoms, prognostic factors and the treatment given.

For the patients treated with curative intent, history, PSA, and DRE are recommended to be performed at 3, 6 and 12 months after treatment and then every 6 months until 3 years, and then annually.

**II.5.1 GENETIC STUDIES ABOUT PROSTATE CANCER**

Prostate cancer represents a pathology of high interest for the whole world, being considered the most frequent cancer of man, occupying second place when considering mortality, after lung cancer.

We do not have clear explanations about the etiology, but the academic world have noticed from many studies that a genetic issue could be responsible, according to the fact that chances of male relatives to develop prostate cancer are at least 4 times higher than in the general population. If the wife of the patient develop breast cancer, the chances for the son to develop prostate cancer are even higher. So, regarding the statistics, it must be a good place to look into the genetic configuration of the patient to find out if there are specific modifications which can explain the appearance of this pathology, on one hand and on the other, the aggressivity of the type of prostate cancer discovered.

I must confess I had a great opportunity to be member of a romanian team which had succesfully included more than 1000 patients detected with prostate cancer from Romania who were analysed in comparison with other 1000 male without any sign (clinical or PSA) of the prostate cancer.

The results were published in the article: A COMPREHENSIVE ANALYSIS OF GENOME-WIDE ASSOCIATION STUDIES TO IDENTIFY PROSTATE CANCER SUSCEPTIBILITY LOCI FOR THE ROMANIAN POPULATION, in Romanian Journal of Morphology and Embriology, in 2016.

Genome wide association studies (GWASs) have made important steps in defining the genes may be considered with a key role in this pathology.

The study included a total of 239 unique single nucleotide polymorphisms. A complete list of RS (reference SNP cluster ID) names, p-values and odd ratios can be found in Table 1.

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Table 1 – Complete list of 239 unique single nucleotide polymorphisms associated with prostate cancer (NR: Not reported)
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Out of 34 SNPs examined by the previously mentioned study, 28 SNPs were found
(rs5945572, rs12621278, rs1465618, rs721048, rs2660753, rs10934853, rs7679673,
rs17021918, rs12500426, rs9364554, rs6465657, rs104 86567, rs445114, rs1447295,
rs6983267, rs16902094, rs16901979, rs1512268, rs4962416, rs10993994, rs112 28565,
rs7127900, rs1859962, rs4430796, rs2735839, rs8102476, rs5759167, rs9623117) in our study results. Rs5945572 located on Xp11.22 was found in our collected database as the results of the paper “Common sequence variants on 2p15 and Xp11.22 confer susceptibility to prostate cancer” with the risk allele frequency of 0.35 and a p-value of 4×10-13 in an initial cohort of 1854 European ancestry cases, 21 372 European ancestry controls and was replicated in a second cohort of 8239 European ancestry cases, 7590 European ancestry controls [48]. In the same results, we also found rs721048 located on 2p15 with the risk allele frequency of 0.19 and a p-value of 8×10-9. Rs12621278 located on 2q31.1 was found in the results of the paper “Identification of seven new prostate cancer susceptibility loci through a genome-wide association study” with the risk allele frequency of 0.94 and a p-value of 9×10-23 in an initial cohort of 1854 European ancestry cases, 1894 European ancestry controls and was replicated in a second cohort of 3268 European ancestry cases, 3366 European ancestry controls. Rs10934853 located on 3q21.3 was identified as a result from the paper “Genome-wide association and replication studies identify four variants associated with prostate cancer susceptibility” with the risk allele frequency of 0.28 and a p-value of 3×10-8 in an initial cohort of 19 879 cases and 18 761 controls of European, East Asian, African-American, Latino, and Hawaiian ancestry. Rs1465618 located on 2p21 was found in the same paper as rs12621278 with the risk allele frequency of 0.23 and a p-value of 2×10-8 in the same initial cohort and replicated in the same second cohort. Rs2660753 located on 3p12.1 was found in our study as a result reported in the paper “Multiple newly identified loci associated with prostate cancer susceptibility” with the risk allele frequency of 1.11 and a p-value of 3×10-8 in an initial cohort of 1854 European ancestry cases, 1894 European ancestry controls and replicated in a second cohort of 3268 European ancestry cases, 3366 European ancestry controls. Rs10934853 located on 3q21.3 was identified as a result from the paper “Genome-wide association and replication studies identify four variants associated with prostate cancer susceptibility” with the risk allele frequency of 0.28 and a p-value of 3×10-8 in a initial cohort of 1968 European ancestry cases, 35 382 European ancestry controls and was replicated in a second cohort of 11 806 European ancestry cases, 12 387 European ancestry controls [47].

Knowledge of a large number of genetic variants correlated with prostate cancer susceptibility and understanding the biological pathways and interactions, which take place at a molecular level between them, would provide important information for possibly preventing “the setting off” of the disease. At the same time, mapping the genetic prostate cancer predisposition provides great progress in developing new-targeted individualized therapies and management strategies.

Identifying a list of clinically relevant genetic markers for predisposition to prostate cancer can also lead to develop of guidelines for genetic testing in order to achieve an effective prevention. The need for a review of previously published single nucleotide polymorphisms (SNPs) associated with prostate cancer that show a strong association with the same phenotype in the Romanian population is needed as a starting point for further research. Our study illustrates the value of combining multiple GWAS results into a larger database that can be easily accessed, updated and modified to reflect the known markers associated with prostate cancer.

Hence, prostate cancer is one of the main causes of death in the male population worldwide, it is very important for clinicians to have the possibility of identifying men with higher risk for the disease for targeted screening methods. Since most of these SNPs do not act individually, the use of risk profiling models could provide important information on the severity, stage of development and spread of the cancer and at the same time for detecting the disease at an earlier stage. For assembling risk profile models for the Romanian population,
supporting the actual validity of GWAS results is needed. Our study provides a starting point for confirming markers identified in future genome-wide association studies for prostate cancer.
II.5.2. REBIOPSY IN THE DIAGNOSTIC OF PROSTATE CANCER

As active urologists, me and my colleagues have been confronted many times with a perfid situation when (based on a clinical, imagistic or laboratory suspicion) we performed a prostatic ultrasound guided biopsy and, despite all the suspicions, the result did not confirm the prostate cancer.

Starting from all the frustration in detecting patients in the early stages with prostate cancer we have made a team of researchers from three universities from Romania, Tîrgu Mures, Iași and Craiova we managed to collect all the information into an article THE PLACE OF REBIOPSY IN THE DIAGNOSIS OF PROSTATE CANCER, published in Romanian Journal of Morphology and Embriology, in 2014.

Urology advanced a lot when the technique of ultrasound guided prostatic biopsy was introduced in daily practice. But despite the huge progress the method can not guarantee 100% accurate results. So the question remains: Did we miss the area with possible prostate cancer lesions?

More than two-thirds of the 1525 cases were diagnosed as PCa on the first biopsy, while the other cases were subdivided into ASAP, HGPIN, and benign. This latter category included normal tissue, inflammatory lesions, and prostate atrophy. The distribution is presented in Figure 1. It should be mentioned that the features of ASAP or HGPIN were observed in 11 other cases but in association with a malignant proliferation, so these cases were included in the (1) cancer group.

Figure 1. Distribution of cases according to histological findings on the first biopsy

There was little variations in the mean age of patients diagnosed with benign, ASAP, HGPIN or PCa. There were no significant differences among the four main subgroups of lesions regarding the mean value of the prostate volume (Table 1). tPSA levels were generally higher than normal. However, it can be noticed that benign lesions and ASAP had a mean value around 10 ng/mL whereas HGPIN and Pca had mean values over 15 ng/mL, with higher levels in PCa (Table 1). The analysis of the number of positive cores revealed that the suspicious foci or the preneoplastic glands are observed on one or two cores while in PCa
cases a mean number of 6.4 cores are involved (Table 1).

Table 1. Mean values of the main assessed parameters in studies subgroups

<table>
<thead>
<tr>
<th>Histopathological aspect</th>
<th>Age [years]</th>
<th>Volume [mL]</th>
<th>PSA [ng/mL]</th>
<th>No. of positive cores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>69.12</td>
<td>40</td>
<td>10.02</td>
<td>-</td>
</tr>
<tr>
<td>ASAP</td>
<td>69.5</td>
<td>42</td>
<td>9.82</td>
<td>1.2</td>
</tr>
<tr>
<td>HGPIN</td>
<td>70</td>
<td>41</td>
<td>16.3</td>
<td>1.9</td>
</tr>
<tr>
<td>PCa</td>
<td>71</td>
<td>41</td>
<td>23.2</td>
<td>6.4</td>
</tr>
</tbody>
</table>

For the 52 cases classified in ASAP category, a second biopsy became mandatory in order to clarify the diagnosis. Thirty-five patients did not present for follow-up examinations, despite telephone or written invitation. Thus, rebiopsy was performed in 17 cases. PCa was detected on the second biopsy specimens stained with HE in seven cases. In two of these, the Gleason score was 6 (3+3), four other cases had Gleason score 7 (3+4 or 4+3) and, in the last case, a high-grade PCa, with Gleason score 9, composed of pattern 4 and 5 was observed. In the remaining 10 cases, the second biopsy specimens displayed normal histological aspect.

TRUS-guided needle biopsy is currently the most reliable method to ensure accurate sampling of prostate tissue in men for harboring prostate cancer based on DRE and tPSA findings. In our study, the TRUS-guided needle biopsy was performed according to the 2013 European Association of Urology Guidelines, i.e.: increased or rising PSA level, abnormal DRE findings. The first elevated PSA level should not prompt an immediate biopsy; it should be verified after a few weeks by the same assay under standardized conditions, in the same diagnostic laboratory, using the same method. Our results confirm the general agreement that, on one hand, the cancer can be present in cases with low tPSA values and, on the other hand, a high PSA value does not necessarily indicate the presence of PCa.

Concerning the technique, there is no consensus about the optimal number of cores that should be taken, the general idea being, as we mentioned above, - the younger the patient and the bigger the prostate, more cores are neededl, meaning that even more than 12 cores can be performed at the initial biopsy. According to the recommendations of Vienna nomogram, we performed between six and 24 biopsies. Regarding the efficiency of the PCa detection rate at the first biopsy, our value of 69.77% is within the range reported in the literature.

PCa diagnosis is the result of a complex algorithm including DRE, tPSA, TRUS and TRUS-guided prostate biopsy. TRUS-guided prostate biopsy is the key step of this algorithm because it is the only examination which confirms the diagnosis of PCa. ASAP in a biopsy specimen is a significant predictor for PCa. Rebiopsy is indicated in these cases especially when there is a solid clinical suspicion of PCa.
II.6. RENAL FAILURE

Acute renal failure (ARF) is characterized by rapid reduction of renal filtration, followed by a rapid rise of serum creatinine concentration, azotemia and disorders of hydro-electrolytic homeostasis.

Anuria is defined as the absence of diuresis, or a diuresis lower than 100 ml per 24 hours.

ETIOLOGY

The mechanism behind glomerular filtration is the pressure gradient from the glomerulus to the Bowman’s capsule space. The common pathogenesis pathway for acute renal failure is represented by the reduction of renal blood flow (RBF).

There are three main causes of acute renal failure:

• Pre-renal causes;
• Renal intrinsic causes;
• Post-renal causes.

Pre-renal failure

In pre-renal failure, the glomerular and tubular function is normal, but the glomerular filtration rate (GFR) is reduced due to the reduction of renal vascular perfusion. It is the most frequent cause of ARF and may lead to intrinsic failure if it is not rapidly corrected. The most significant factors that can reduce GFR are:

• volume depletion due to diuretics, polyuria, vomiting, diarrhea, hemorrhagic shock, or extended burns;
• fluid losses into the extravascular spaces (peritonitis, ileus, pancreatitis);
• decreased cardiac output due to myocardial infarction, cardiogenic shock, congestive heart failure, pulmonary embolism;
• systemic vasodilatation due to drug overdoses, sepsis, anaphylaxis;
• afferent arteriolar vasoconstriction due to hypercalcemia, anti-inflammatory drugs, norepinephrine, hepato-renal syndrome.

Renal intrinsic failure

The most common underlying reason of intrinsic failure is acute tubular necrosis, due to ischemic and cytotoxic factors. The most frequent causes of intrinsic failure are:

• acute tubular necrosis (ischemic or toxic);
• acute cortical necrosis;
• vascular causes, including renal vessels obstruction, microangiopathy, malignant hypertension, pregnancy toxemia, lupus and advanced atherosclerosis;
• glomerulonephritis of various origins;
• tubular causes, as intravascular hemolysis, rhabdomyolysis;
• interstitial causes, including pyelonephritis, systemic diseases, and drug poisoning.
Post-renal failure

Post-renal failure occurs due to mechanical obstruction of the urinary collecting system, which can be bilateral, or unilateral (in case of a contralateral non-functioning kidney). The main cause of post-renal failure is ureteral obstruction, due to obstructive lithiasis, tumors, accidental ureter ligature – gynecological interventions, or fibrosis.

PATHOPHYSIOLOGY

The reduction of RBF leads to cell ischemia, triggering a cascade of events including the production of free radicals and cytokines, followed by endothelial activation, leukocyte adhesion, activation of coagulation and apoptosis. Finally, tubular damage occurs, facilitating the reversal of glomerular filtration and the further reduction of GFR. Dying cells accumulate into the tubules, forming an obstructing cast, which also reduces GFR, which manifests clinically as oliguria/anuria. This process of cell injury continues even after the normalization of RBF.

The process of recovery from ARF is closely dependent by RBF: the sooner RBF is restored, the better the recovery prognosis is warranted. After the restoration of RBF, the remaining functional parenchyma increases its filtration function, trying to compensate for the nephron loss.

CLINICAL PRESENTATION

Medical history should document any causes, including lithiasis, tumors, infection, trauma, shock, hemolysis, and specific drug intake. Oliguria (100-400 ml urine/day) is a common finding, but in some cases the urine volume is normal, or the patient may have even polyuria (in intrinsic ARF).

Complete absence of urine (anuria, <100 ml/day) is suggestive of post-renal ARF, or for severe acute tubular necrosis. Frequently occurring symptoms of edema, hypertension and heart failure are caused by water and salt retention. Finally, uremia is associated with acidosis, dyspnea, nausea and vomiting, up to encephalopathy and coma.

PARACLINIC INVESTIGATIONS

- blood tests: complete blood count, serum creatinine, blood urea nitrogen, uric acid, creatinine clearance;
- urinalysis and urine electrolytes;
- abdominal ultrasonography and Doppler ultrasonography;
- radionuclide imaging (isotopic renogram) and magnetic resonance imaging (MRI).

STAGES OF ARF

1. Pre-anuria phase (renal aggression):
   - between 24 hours and several days;
   - clinical symptoms of the underlying disease.
2. Oligo-anuria installation phase:
   • 24 – 72 hours;
   • fluid retention with edema, dyspnea, weight gain;
   • elevations of serum creatinine and urea.

3. Oligo-anuria phase:
   • 7 – 21 days;
   • systemic manifestations: cardiovascular, neurological, respiratory, skin.

4. Poliuria (diuresis recovery) phase:
   • 8 – 10 days;
   • recovery of diuresis: up to 3 – 4 l/24 h;
   • improvement of general status;
   • significant weight loss;
   • slow decrease of serum creatinine and urea, after initial increase due to dehydration induced by polyuria;
   • electrolyte losses could be significant and supplementation therapy is necessary.

5. Functional recovery phase:
   • 3 – 12 months;
   • initial polyuria: a high fluid input is necessary;
   • glomerular filtration is initially recovered, followed by the recovery of concentration capacity.

MANAGEMENT OF ACUTE RENAL FAILURE

Therapy should be initiated as soon as possible, trying to correct the identifiable causes of ARF, as hypovolemia, or obstruction. Conservative measures include monitoring and maintenance of fluid homeostasis, corrections of electrolytes and acid-base balance (acidosis, hyperkalemia, hyponatremia and hypocalcemia), and protein intake restrictions.

Despite the mentioned conservative measures, a significant proportion of patients will need dialysis, as a final solution to prevent major health damage. The main indications for dialysis are:
   • Body fluid overload, leading to pulmonary edema (Central Venous Pressure > 16 cm H2O);
   • Severe hyperkalemia (K+ > 6.5 mEq/l);
   • Severe metabolic acidosis (alkaline reserve <15mmol/l);
   • High azotemia and uremia (urea >240 mg/dL, creatinine >10 mg/dL);
   • Uremic encephalopathy;
   • Deterioration of clinical status, including nausea and confusion.

PROGNOSIS

The mortality rate associated with ARF is 30-60%. If the patients need dialysis, the mortality rate is up to 90%. The prognostic factors include the:
   • Cause of ARF;
Patients age;
• Severity of ARF;
• Associated pathology;
• Complications.

**OBSTRUCTIVE ANURIA DEFINITION**

Obstructive anuria is defined as the absence of urine in the bladder due to an obstruction at the level of the ureter, causing acute post-renal failure. The obstruction could be intrinsic (lithiasis, ureter tumors), or extrinsic (invading cancers, bilateral ureter ligation, retroperitoneal fibrosis). Obstructive anuria is more frequent in patients with a solitary kidney (congenital, surgical, or functional).

**DIAGNOSIS**

- Medical history suggestive of urinary lithiasis, neoplasia, recent surgery;
- Palpation of lumbar area is painful;
- The bladder is empty or at the insertion of a catheter we can evacuate few milliliters of hematic / cloudy urine;
- If the anuric patient has fever - this is a high alert emergency;

**IMAGISTIC INVESTIGATIONS**

- Ultrasound can show ureterohydronephrosis on the same side with the lumbar pains or bilateral ureterohydronephrosis; we can measure the renal parenchima or see associated pathology (Tumor?; Limph nodes?; Cyst?; etc.) and the possible associated pathology of the contolateral kidney.
- On KUB we can see opacities in the projection area of the kidney or the ureter, suggestive for radiopaque stones;
- CT scan without contrast is more accurate than KUB and ultrasound;

**PARACLINIC INVESTIGATIONS:**

- elevated blood urea and creatinine;
- elevated K⁺ (attention! If K ≥ 6,5mEq / L - emergency dialysis), elevated phosphates;
- decreased alkaline reserve, decreased Na⁺, decreased Ca⁺.

**THERAPY**

The aim of the therapy in obstructive anuria is to immediately restore the permeability of the urinary system.

- Percutaneous nephrostomy could be performed under radiological or ultrasonographic guidance: one calyx is punctured and a nephrostomy catheter is inserted into the kidney;
- Ureteral catheterization could be achieved by using simple ureteral catheters, or autostatic double J stents, which are inserted into the ureter by cystoscopy, which could also gather diagnostic information regarding the cause of anuria;
- Maintenance of hydro-electrolytic and acido-basic homeostasis, especially after
drainage, when polyuria occurs.

Chronic renal failure (CRF) is a syndrome characterized by the progressive loss of all kidney functions, caused by bilateral kidney damage. The kidney function loss is persistent and irreversible, disturbing body homeostasis at multiple levels, and finally resulting in uremia.

The diagnosis of CRF is confirmed when the patient has values of GFR<60 ml/min/1.73 m², for at least 3 months, with or without renal structural lesions, and changes of blood and urine composition.

EPIDEMIOLOGY
The incidence of CRF has increased constantly during the last 20 years, due to the growing percentage of aging population, and to the increasing incidence of diabetic and hypertensive nephropathy, which are the most common causes. CRF is more frequent in males and in African Americans.

ETIOLOGY
A. Primary glomerular syndromes:
   - Primary glomerulonephritis (membrano-proliferative);
   - Idiopathic focal glomerulosclerosis;
B. Tubulo-interstitial diseases:
   - Heavy metal poisoning (with mercury, lead);
C. Polycystic kidney;
D. Renal vascular diseases:
   - Stenosis of renal arteries (due to atherosclerosis);
   - Bilateral thrombosis of the renal veins;
   - Nephroangiosclerosis due to chronic untreated hypertension;
E. Chronic pyelonephritis;
F. Chronic obstruction of the urinary tract:
   - Lower urinary tract obstruction (benign prostatic hyperplasia, urethral strictures);
   - Upper urinary tract obstruction (bilateral ureteral lithiasis, ureter tumors, retroperitoneal fibrosis);
G. Metabolic diseases:
   - Diabetic nephropathy;
   - Renal amyloidosis;
   - Gout nephropathy;
   - Analgesic nephropathy;
H. Collagen systemic diseases:
   - Lupus;
   - Polyarteritis nodosa;
   - Rheumatoid arthritis.
Evolution of CRF:
- Very fast (maximum 1-2 years) – in rapidly progressive glomerulonephritis, systemic disease, malignant nephroangiosclerosis;
- Fast (4-5 years) – in diabetic nephropathy, mesangio-capillary glomerulonephritis, renal amyloidosis;
- Slow (10-30 years) – in polycystic kidney, congenital anomalies, membranous glomerulonephritis.

PHYSIOPATHOLOGY
Regardless of its etiology, chronic renal failure is the consequence of the destruction of a significant number of functional nephrons. Initially, the kidney has the capacity to maintain an adequate level of GFR, by adaptive mechanisms at the level of remaining functional nephrons. Due to progressive destruction of the remaining nephrons, at a specific time point, the kidney loses its adaptation capacity, resulting in the proportional reduction of GFR.
The normal functions of the kidneys are the following:
- Maintenance of hydro-electrolyte and acido-basic homeostasis;
- Excretion of byproducts of cellular metabolism and toxic substances;
- Control of erythropoiesis;
- Activation of vitamin D3;
- Stabilization of blood pressure.

THE UREMIC SYNDROME
The uremic syndrome is very complex, due to the effects of chronic, generalized intoxication with uremic toxins. It has consequences at multiple levels, affecting the cardiovascular, gastrointestinal, hematopoietic, endocrine and immune systems. The most important prognostic factor of renal failure is proteinuria, which is directly proportional with the severity of CRF; the capacity of glucose metabolization is also affected, and the patient response to insulin administration is impaired.

CLINICAL PRESENTATION
A. Cutaneous symptoms:
   - Dry skin;
   - Urea frost;
   - Pruritus;
   - Pallor;
   - Edema.
B. Gastrointestinal symptoms:
   - Ammonia taste;
   - Uremic odor;
   - Stomatitis, dry mouth;
   - Hiccups;
   - Chronic gastritis;
• Constipation due to dehydration;
• Diarrhea in terminal uremia.

C. Musculo-skeletal symptoms:
• Chronic fatigue;
• Bone pain;

D. Neurological symptoms:
• Headache;
• Insomnia;
• Vertigo;
• Paresthesia;
• Peripheric neuropathy;
• Tremor;
• Convulsions;
• Coma in terminal uremia;

E. Respiratory symptoms:
• Kussmaul acidotic breathing;
• Dyspnea;

F. Cardiovascular syndromes:
• Hypertension;
• Heart failure;
• Uremic pericarditis;
• Arrhythmias;

G. Hematologic modifications:
• Anemia;
• Coagulopathy with bleeding tendency;

H. Immunological disorders:
• Imunosupression;

I. Hypothermia;

J. Eye modifications:
• Uremic retinopathy;
• Red eye due to calcium deposits;
• Uremic amaurosis;

K. Gonadic disorders:
• Impotence;
• Infertility;
• Decreased libido;
• Gynecomastia;
• Menstrual disorders, going to amenorrhea;

L. Endocrine disorders:
• Hyperparathyroidism;
• Increased prolactin;
• Increased renin activity;
• Vitamin D activation deficit;
• Erythropoietin deficit.

PARACLINIC INVESTIGATIONS
• Blood tests: complete blood count, blood urea nitrogen, serum creatinine, uric acid, serum electrolytes, glycemia, serum albumin, lipid profile, serum complement;
• Kidney functional tests: creatinine clearance, GFR;
• Urinalysis, urine osmolarity;
• 24-hour urine: total proteins and urinary creatinine;
• Ophthalmology exam: fundus examination;
• Renal ultrasonography, including Doppler scan;
• Plain abdominal X-ray;
• CT scan/MRI;
• Retrograde cystography;
• I.V. pyelography (if serum creatinine level <2 mg/dL);
• Renal biopsy.

The Cockcroft-Gault formula for GFR calculation:
GFR is calculated using the Cockcroft-Gault formula, based on the level of serum creatinine.

\[
C_{Cr} = \frac{(140 - age) \times \text{weight (kg)}}{72 \times S_{Cr}} \times 0.85 \text{ if female}
\]

\[C_{Cr} = \text{creatinine clearance (expressed in mL/min)}; \quad S_{Cr} = \text{serum creatinine (expressed in mg/dL)}\]

Another formula for GFR calculation is the abbreviated MDRD:

\[GFR = 183 \times (\text{serum creatinine}) - 1,154 \times (\text{age}) - 0,203 \times (0,742 \text{ if female or 1,21 if black})\]

This formula is much easier to use than the calculation of creatinine clearance based also on the values of urinary creatinine.

Normal values:
• Men: 97 – 137 ml/min/1.73 m2;
• Women: 88 -128 ml/min/1.73m2.

STAGES OF CRF
• Stage 1: kidney damage with normal/increased GFR (>90 ml/min/1.73 m2);
• Stage 2: mild reduction of GFR (60-89 ml/min/1.73 m2);
• Stage 3: moderate reduction of GFR (30-59 ml/min/1.73 m2);
• Stage 4: severe reduction of GFR (15-29 ml/min/1.73 m2);
• Stage 5: kidney failure (GFR <15 ml/min/1.73 m2, or dialysis).
STAGE DIAGNOSIS

A. Initial/mild CRF:
   - Asymptomatic;
   - No significant paraclinic modifications;
   - Reduction of renal adaptive mechanisms.

B. Moderate CRF:
   - Compensatory polyuria;
   - Moderate anemia (3.5-4x106/mm3);
   - Serum creatinine between 1.5 – 3.2 mg/dL.

C. Severe CRF
   - Fatigue
   - Acidotic breathing;
   - Dyspnea;
   - Serum creatinine between 3.2 – 7 mg/dL;
   - Anemia (3-3.5x106/mm3).

D. CRF in the uremic stage:
   - Uremic syndrome;
   - Serum creatinine between 7 – 8 mg/dL;
   - Severe anemia (2.5-2.5x106/mm3).

E. End-stage CRF
   - Serum creatinine > 8 mg/dL;
   - Severe anemia (<2.5x106/mm3).

MANAGEMENT OF CRF

A. Actions to delay or stop the progression of CRF:
   - Etiologic treatment of the underlying condition: it has the most significant impact on disease progression/evolution;
   - Blood pressure control with ACE inhibitors or angiotensin receptor blockers;
   - Adequate control of glycemia;
   - Diet with protein and fluid restriction;
   - Avoidance of sustained physical effort;
   - Therapy of hyperlipidemia;
   - Therapy of metabolic acidosis: bicarbonate supplementation;

B. Correction of the disorders associated due to CRF:
   - Anemia: erythropoietin, iron, folic acid, supplementation;
   - Hyperphosphatemia: dietary phosphate restriction, phosphate binders;
   - Hypocalcemia, osteodystrophia: calcium supplements, vitamin D, eventually calcitriol;
   - Pruritus: antihistaminic drugs;
   - Volume overload: loop diuretics;
   - Metabolic acidosis: oral alkali supplementation;
   - Cardiovascular complications: therapy of hypertension, heart failure;
   - Prevention/therapy of infections.
C. Chronic renal replacement therapy (see below).

PROGNOSIS
In general, patients with CRF progress to End Stage Renal Disease (ESRD), needing chronic renal replacement therapy (dialysis and/or renal transplantation). The progression to ESRD depends on the severity of primary diagnosis, but also on the timing of administration of specific therapy. However, the morbidity and mortality rate are significant, especially in patients on chronic dialysis.
II.6.1 VASCULAR CALCIFICATIONS AT PATIENTS WITH CHRONIC RENAL FAILURE

The collaboration between urologists and nephrologists have many beneficial aspects: a large amount of patients with urologic pathologies can become, in time, renal insufficient but also a group of patients with nephrologic pathology can develop complications that need a urological interventions in delicate conditions.

The arterio-venous fistula, a borderline between the two specialities, usually made by the urologist or the vascular surgeon, is an intervention that permits the patient to be enrolled in the dialysis programme until the chance of renal transplantation occurs.

So, in this study, VASCULAR CALCIFICATIONS IN CONTINUOUS AMBULATORY PERITONEAL DIALYSIS PATIENTS published in the Romanian Journal of Morphology and Embriology, in 2015, we had explored the vascular calcifications which are considered to be a severe complication of chronic renal failure in the final stages.

Despite all the progresses we have made so far to underestant the mechanism of these agressive and deadly complications there are many things to be discovered.

During a prospective three-year study (between October 2009 and September 2012), conducted in our Department of Nephrology and Dialysis, –St. John Emergency Clinical Hospital, Bucharest, Romania, 21 CAPD patients with secondary hyperparathyroidism were selected. At the moment of inclusion, the subjects had a history of at least three months of dialysis, they were over 18 years, they had signed the Patient Informed Consent and all the data was assessed according to our University Ethic and Research Committee. All individuals performed four exchanges per day, 19 patients with 2 liters/exchange and 2 with 1.5 liters/exchange. The median age was 57 years, with limits between 33–79 years. Male:female ratio was 15:6. Patients who had primary hyperparathyroidism, sarcoidosis, myeloma, neoplastic diseases, diabetic nephropaty as a primary renal disease, renal transplantation, transfered in other dialysis centers or even death during the study were excluded.

At the beginning of our research, the following information was collected from personal medical history or from hospital documents: age, gender, primary renal disease, years of dialysis, cardiovascular comorbidities. Additionally, all patients underwent a protocol of clinical laboratory tests. Dialysis efficiency was tested with Kt/V and peritoneal equilibration test that was performed at three or six months, afterwards.

A positive correlation was noticed for all 21 CAPD patients between aortic calcification scores K1 and K2 and time on dialysis (Figure 1), but no statistical association between these scores and patient’s age (Figure 2).

In the beginning, the presence of vascular calcifications (K1≥1) was noted in 18 (85.71%) patients; median K1 value was 8.55, with limits between 1 and 18. After three years, 20 (95.24%) patients had vascular calcifications (K2≥1); median K2 value was 10.2, with limits between 2 and 20 (Figure 3). The median increase of Kauppila score was 2.5, ranging between 1 and 4.
Contrary to other researches [47-50], in our study the patient’s age was not a risk factor for VC development. An explanation of this finding may be a younger median age in our cohort of patients. Although in literature is stipulated that VC may occur in older patients in the absence of renal failure [51, 52], it is also emphasized that the patterns of the
calcifications are different in these two situations [52,53]. The methods used in our trial to reveal the degree of VC cannot make the difference between intimal and medial calcifications, but this was a limitation of other researches, too [54].

The observations regarding the correlation between serum calcium and/or Ca×P product and VC are controversial [47,55]. Most studies highlighted a positive connection between high serum calcium and/or high Ca×P product and the development of VC [47,56]. In our study, we did not find a positive association: the development or aggravation of VC was positive correlated only with high phosphorus, but not with low phosphorus, high/low corrected serum calcium or high Ca×P product.

These findings may be explained by the coexistence of additional factors specific for peritoneal dialysis, which contribute to the development of VC: hyperlipidemia, peritoneal calcifications, and high-glucose solution abuse.

Time on dialysis, high serum phosphorus, high values of iPTH, high C-reactive protein, chronic tubulointerstitial nephropathies were the main factors positive correlated with VC in our CAPD patients. No association between VC and Ca×P product, serum calcium, albumin or bicarbonate was found. Further researches are needed in order to identify factors influencing development of VC in peritoneal dialysis population.
II.6.2. PERMANENT VASCULAR ACCESS IN HEMODIALYZED PATIENTS

The arteri-venous fistula, a border line between the two specialties, urology and nephrology is the arterio-venous fistula, made most of the time by the urologists or the vascular surgeons, permits the patient to be enrolled in the dialysis programme until the chance of renal transplant occurs.

The vascular access is still a delicate issue on the long list of problems of the chronic renal failure patient.

In the article AN OVERVIEW OF PERMANENT VASCULAR ACCESS IN HEMODIALYZED PATIENTS published in the Romanian Journal of Morphology and Embriology, in 2015, we make an analysis of this problem, essential for the survival of the patients.

In the last decades, there have been important improvements of hemodialyzed (HD) patients’ prognosis due to the possibility of vascular access development and performing dialysis using arteriovenous fistula (AVF). The burden problem of medical team is represented by early (within three months since the initiation moment and late complications caused by AVF per se. According to DOQI (Disease Outcome Quality Initiative) recommendations, a suitable AVF presents the following features: flow >600 mL/min. and diameter >0.6 cm.

It was observed that in 23–46% cases, AVF early failure develops and the pattern lesion, noticed also in late complications, is vascular stenosis. Additionally, there are still important questions regarding the pathophysiological mechanisms incriminated in AVF early failure setting:

→ neointimal hyperplasia – caused by increased levels of transforming growth factor β(TGF-β), insulin-like growth factor or other markers of oxidative stress;

→ significant vascular remodeling – induced by the presence of SMA+ve, vimentin+ve, desmin-ve myo- fibroblast or abnormal changes of smooth muscle and endothelial cells.

Furthermore, as different clinical and experimental trials concluded, there is a clear association among blood stream, shear stress (frictional force exerted by blood on the vessel wall, transmural pressure and intimal thickening with direct impact on AVF failure development.

Summarizing, during AVF maturation period several mechanisms are involved: elevated blood flow inducing increased shear stress on vessel wall, exacerbation of oxidative stress with direct impact on arterial and venous dilatation and high pressure of venous segment.

Although there is a wide range of treatment options for AVF failure resolution, prophylaxis is essential not only for preventing, but also for choosing the suitable anatomical segment for performing a vascular access. As previous trials have indicated B-mode high-resolution ultrasonography (using a 12.5 MHz transducer) may provide useful information and detect abnormal features of patients’ vessels.

Particular in Romania, as in all the countries without a high-developed renal transplant
system, the importance of a stable and reliable chronic vascular access must be the key point of the management of the ESRD patient. Achieving an early-particularized vascular access for each patient in need of renal replacement therapy is the adequate solution for a better control of this pathology and prevention of AVF early and late complications. For this reason, an adequate AVF can be considered – the Achilles’ heel of hemodialysis‖ and a multidisciplinary approach is essential for creating and maintaining vascular access in optimal parameters.
II.6.3 VITAMIN K IN HEMODIALYSED PATIENTS

Cardiovascular disease causes increased mortality in chronic hemodialysed patients. The decrease of vascular calcification is one of the main targets in the management of these patients. In the article Vitamin K Influence on Cardiovascular Mortality in Chronic Hemodialysed Patients, published in Revista de Chimie (Bucharest) in 2017 we have evaluated the improved prognosis and decreased mortality of vitamin K supplements, in chronic hemodialysed patients.

Recent trials support the beneficial role of food vitamins in reducing the cardiovascular risk in hemodialysed patients. Vitamin K is mentioned among the vitamins that have a role in improving cardiovascular risk by reducing calcification in chronic hemodialysed patients.

In 1930, Henrik Dam described for the first time the existence of vitamin K, and subsequent studies confirmed its role in blood coagulation (clotting). Vitamin K belongs to the class of fat soluble vitamins (absorption requires the presence of fat), naturally presenting in the following forms: vitamin K1 (phylloquinone) and different types of vitamin K2 (menaquinone). The primary structure represented by methylated naphthoquinone is specific to all the class members, differentiation being made through the aliphatic chains linked to the nucleus in different positions. Vitamin K (C11H7O2-R), vitamin K1 (C31H46O2), and vitamin K2 with radicals C30H49, C35H57, C45H73 are represented in the following figures (figs. 1, 2 and 3). The natural sources of vitamin K1 and vitamin K2 differ.

Vitamin K1 synthesis occurs in plants, while vitamin K2 synthesis takes place in the human body, in the presence of bacterial flora. Vitamin K is useful in the glutamate (Glu) carboxylation process, present in the constitution of various proteins, resulting in gamma-carboxylglutamate (Gla) (fig. 4). There are various proteins which contain Gla, among which prothrombin, coagulation factors VII, IX and X, protein C, protein S, osteocalcin, matrix Gla protein etc. In chronic kidney disease patients, matrix Gla protein and osteocalcin (vitamin K dependent proteins) are important in the process of vascular calcification, being recognized as some of the most potent inhibitors of vascular calcification.

Matrix Gla protein is present in the vascular endothelium, being produced by the smooth muscle cells. It is activated in the presence of vitamin K. Gla proteins are preferentially carboxylated and in patients with vitamin K deficiency extrahepatic located Gla proteins (e.g.: matrix Gla protein, osteocalcin) are found in carboxylated form in a lower percentage compared to those hepatic located (e.g.: prothrombin, coagulation factors VII, IX and X).
The quantification of the level of uncarboxylated Gla proteins (especially the extrahepatic ones) helps for detecting the patients with vitamin K deficiency. Furthermore, the increased level of uncarboxylated Gla proteins is associated with important arterial calcification and subsequently with an increased risk of cardiovascular mortality. Osteocalcin is found in bones, being produced by osteoblasts, and it is used as a marker for bone formation.
The level of uncarboxylated osteocalcin is also useful in detecting patients with vitamin K deficiency. In addition, there are some studies highlighting that initially increased undercarboxylated matrix Gla proteins levels decreases in advanced chronic renal failure and it does not further elevate as it would expected; therefore, reasonable doubts arouse regarding the utility of using the undercarboxylated matrix Gla protein as a marker for vitamin K deficiency. Several explanations of this phenomena have been developed. One is that the undercarboxylated matrix Gla protein is accumulated in the calcified areas, but the most probable explanation is that matrix Gla protein, in contrast with osteocalcin, undergoes also concomitant vitamin K-dependent ß-glutamate carboxylation and serine phosphorylation.

Therefore, undercarboxylated matrix Gla protein exists under two forms: phosphorylated and nonphosphorylated, and only the nonphosphorylated fraction, which is approximately 1000 times lower than total undercarboxylated matrix Gla protein, is an adequate marker for vitamin K deficiency. Gamma-carboxylated matrix protein inhibits vascular calcification by combining with insoluble salts of calcium, thus preventing vascular hydroxyapatite crystal growth. Additionally, it inhibits the action of the BMP (bone morphogenetic protein) at vascular level. In patients with chronic kidney disease and mineral-bone disorders, BMP promotes the phenotypic transformation of endothelial smooth muscle cells into osteoblast-like cells, and, consequently, by inhibiting it, vascular calcification is prevented.

For the carboxylation of proteins involved in vascular calcification, vitamin K serum level is an important factor. Among the types of vitamin K, vitamin K2 has the most important role in the gamma carboxylation. Food that provide vitamin K2 are fermented food, fermented cheese, meat, meat offal, egg yolks, etc. In chronic hemodialysed patients, who require a diet with low phosphorus amount, vitamin K2 intake and serum levels are reduced; no removal by dialysis procedure is present because vitamin K is lipophilic. Although vitamin K2 may derive from vitamin K1 in the so-called vitamin K cycle, it is proved that in chronic kidney disease and end-stage renal disease, vitamin K recycling is impaired and may be restored by increased doses of vitamin K1.

Supplementation with high doses of vitamin K1 is regarded with circumspection, because it is also decreases the osteocalcin; undercarboxylated osteocalcin has been associated, in experimental studies, with positive effects on glucose metabolism and on regulation of male fertility. Therefore, to avoid vitamin K deficiency it is important that these patients follow a low phosphorus diet, but with vitamin K2 intake. In this category there are: goat cheese, camembert, butter cream, etc.

Given the important role of vitamin K2 in reducing vascular calcification, many recent studies recommend supplements of vitamin K2 in chronic hemodialysed patients, but the optimal doses of vitamin K supplementation in hemodialysed population are not yet well established. Following the administration of these supplements, it was noticed that the level of Gla uncarboxylated protein (inactive) was reduced and the prognostic improved in these individuals by decreasing cardiovascular death risk. Favorable effects of vitamin K2 supplementation have been noted on bone remodeling too, including adynamic bone disease in hemodialysed patients.

Although the available data regarding the importance of vitamin K supplementation in reducing vascular calcification development in hemodialysed population are promising,
further larger clinical trials are needed in order to establish the required doses for the best adequate effect.

III. FUTURE RESEARCH AND DIRECTIONS

III.1. PLANS FOR FUTURE RESEARCH

The plans for my future directions of research are connected with the day by day activity in my department in order to find out solutions for the dilemmas we have.

I have started this plan having in mind a simple fact which makes all the difference: the vast majority of studies published up to now in important medical journals are based on the realities of population groups for the anglo-saxons countries, groups which are different from Romanian population regarding the health care education, periodic health control, instruction follow up regarding diet or medication, etc. This fact makes almost impossible to apply the results of anglo-saxons studies in the realities of our country.

III.2. ACADEMIC AND POSTGRADUATE FUTURE DEVELOPMENTS

III.2.1 PREVENTION OF DOUBLE J INCRUSTATION

With this purpose I would like to dedicate my efforts to producing a study which I hope will emphasize different aspects concerning the most efficient methods to block the process that leads to incrustation of the double J stents that are used for many months, using different drugs which in my opinion may bring benefits. In modern days practice, stenting is represented by the insertion of a device which realises a way of acces in the cavitarian organs where an obstacle is blocking the way (from the interior – e.g. a stone or from exterior – e.g. a tumor compression).

The name „stent‖ comes from an english dentist named Charles Thomas Stent (1807 - 1885), who invented a metal device used in medical practice to fix the tissues. After this discovery different devices produced to mentain vascular permeability were named after him [49].

In 1967 Zimskind and co. have reported the use of ureteral stents made by silicon and inserted with endourologic procedures.

These were in fact tubes connected to a 4 fr. catheter which were displaced after the endoscopic manœuvre, and the authors had observed the benefits over the urinary tract infections and the possibility to use the stent for a longer period of time.

In 1978 Dr. Roy P Finney has modified the simple stent adding 2 loops thus giving it the name we know today, double J stents. This was a huge step forward for the development of endoscopic ureteric intervention.

Double J stents can be used in the first place to treat an ureteric obstruction or on a larger scale in more laborious ureteral intervention (retrograde or anterograde ureteroscopy, dilatation of the ureteral stenosis, endopyelotomy, etc.) or after classical surgery intervention with lesions of the ureter, infected hydronephrosis, etc. [50].
The ideal double J stent does not exist yet although any urologic department in the world uses this device on a daily basis. The characteristics of an ideal JJ stent would be:

- Price friendly;
- Easy to configure;
- Biocompatibility;
- Easy to tolerate by the patient;
- Denying the adherence of germs or other mineral components found in urine in this way delaying the incrustation [51].

Having this goals in mind, researchers all over the world have used different materials for the double J stents: poliethylen, politetrafluoroethyilen (PTFE), poliurethan, vynil policiolor, elastomer thermoplastic stirenic, silicon, natural rubber [50-54]. They discovered that once inserted in the urinary tract, the life of a double J stent is shorter, because of the biofilm which appers on the surface, as a first step to the incrustation. This incrustation is dangerous for several reasons: first of all it can injure the urothelium, second of all it can diminuate the elasticity of the stent, which will never be removed as a normal one. More of that they discovered that the aromathic polyuretans can desintegrate and the resulting compounds can be toxic [55,56].

The stents are different, with various dimensions and diameters, between 4,7 fr. and 18 fr. with the lengh between 12 and 32 cm. The distal loop can be simple or double and it is highly recomended to adapt the lengh of the stent at the dimensions of the patient.

The urinary tract infection is the result of the interaction between the uropathogens and the human body. There are several ways for the germs to get into the urinary system which is protected by several natural mechanisms to be germ free: the ascending route (from the bowel reservoir, vagina or perineal skin) ascent through the urethra into the bladder and then through ureter to the renal pelvis. The hematogenous route determine renal abcess (mostly with Staphilococus aureus) and the lymphatic route determine retroperitoneal abcesses [57].

The contamination of the urinary tract with different germs can happen during different interventions (inserting catheters, etc.) or through the manipulation/desintegration of stones containing germs that will grow in this ideal place.

The attachment of E.coli bacteria to the ureteric stent is a hypothesis little known and discussed but, in my view it needs a special atention because E.coli has the phimbria, the special component that permits the bacteria to attach to the bladder mucosa. The catheter infection can induce fever, lumbar pain, digestive signs, an influenced general status and in those cases a prompt intervention is needed: antibiotics, replacement or supression of the stent ,etc. [58,59].

Mulhall and Slade have noticed since 1980 that for the patients with ureteric stents the infection risk is higher (5-8% per day) and 90% of the patients will develop bacteriuria in 4 weeks [60,61].

Mulhall, Keane and Reid have reported that, on the long term, 50% of the ureteral stents inserted for a longer period of time will present incrustations [61,62]. The colonisation with bacteria of the ureteral stents is observed in 28%-90% of the cases studied by Kaper and Donlan [63,64].

This colonisation of the stent is not accompanied by a positive urinalysis. Riedl and co. have reported the colonisation of the stents in 69.3% of the cases but the urinalysis
was positive in 42.5% of the cases. The same results were obtained by Rahman and co. on a group of 100 patients, so the urinalysis is not the ideal indicator of the presence of the germs in the catheter [65].

In order to avoid the occurrence of the urinary tract infection and the incrustation of the stents we do not have other option but to administrate the antibacterial agents even though there is a high risk of inducing multi drug resistance. In special cases the therapy must be completed with the supression of the stent in order to treat the infection more efficient. The incrustation can be seen in patients with both infected urinary tract systems and sterile systems [66].

The prevention of biofilm occurrence on the stent is not a process fully understood and despite the progresses both in vivo and in vitro, no matter what antimicrobial agent were used, we still do not know a lot of things about infection and incrustation and the resistance of the germs remains also a delicate issue [67].

Stickler and co. have investigated the stents used for approx. 12 weeks and they have notice a low rate of colonisation and incrustation for stents that contain metacriloloxietietilfosforilcoline, stents having almost the same surface characteristics as the red blood cells [68,69].

It is clear that future research are orientation towards the modification of the surface of the stents is in order and they have to include new inhibitors of the biomolecules and inhibitors of bacterial adherence.

It was demonstrated by Costerton and Probert that E.coli has the possibility to induce and form biofilms both in vivo and in vitro [70,71] and E.coli is the most frequent pathogen in the UTI, responsible for more than 80% of the urinary tract infections. [72,73].

The interest for the E.coli as leading actor in this process of controlling the biofilm has grown in the last years because of complexity and versatility of this germs at the antibiotic action. E.coli has more than 250 setotypes from the inofensive intestinal variants to the very aggressive ones including species that prefer the colonization of medical devices.

The study published by Prott and Kloter using the E.coli model in producing the biofilm has shown that the mobility and not the chemotaxy was the main issue.

On the other side Pringent - Combaret and co. concluded that not mobility is the main problem but the adhesion of plasmide secreted by E.coli, in the absence of phimbrie [75].

From what I have presented the results are very clear that modern urology is linked to the double J stents but, at the same time, the double J insertion for a longer period of time put the patient in danger for the urinary tract infection and incrustation of the stent with all the negative facts coming from this complication. Searching for a drug, already existing in pharmacy, with the special goal to prevent the biofilm and incrustation is the main goal of our study.

In our study wanted to observe if the drug Uractiv Litho used for the prevention of E.coli adherence to the double J stents is similar to the Cranberry extract which has a demonstrated role in preventing the adherence of the E.coli to the bladder mucosa. So we do not prefer antibiotic administration because it is known that the biofilm is resistant in exchange we would prescribe medication to prevent cristalisation in the urine or
medication that prevents the adherence of the bacteria to the bladder mucosa.

Why are we focusing our efforts on this? Because it is known that in the reversible phase of bacterial adherence, the antibiotic and antibiofilm components are the most efficient because the bacteria has not formed the matrix yet and they are „vulnerable” at the antibiotic action. Once the attachment of the bacteria is irreversible, the biofilm is far more resistant to antibiotics or the immune system reaction [76].

The strategy for determine the best method of treatment to prevent the biofilm or secondary incrustation represents a challenge and a necessity at the same time. We are looking forward to finding out accessible treatments with less side effects and toxicity, because a long term antibio prophylaxis, for 3 months is not justified and cannot be done.

I have decided to start this study for several reasons:
- Up to present day there is no knowledge about a medical treatment capable to prevent 100% the occurrence of the biofilm on the stent, even in the cases when the “JJ” insertion were made without any infectious context (obstructive ureteric stones with high intensity renal colic at patients without any infection prior to the insertion of the double J stent).

The two medications we want to study and compare are already in drug stores and they have been used for many years for patients with stones and urinary tract infections (UTI). They have minor side effects and there is no mention about toxic events. First of them is *Phyllanthus niruri* and it has a long reputation to dissolve the calculi in the urinary system, so we can presume that this drug known by centuries can play a key role in blocking the development of the matrical zones on the JJ surface.

Regarding the prevention of the UTI using different molecules or compounds the anti-adherence problem is now a certain preocupation for researchers who want to prevent the recurrence of the UTI, mainly with *E.coli* [77].

The second drug, the cranberry extract, which is a member of the *Ericaceeae plants*, is the only phitoterapeutic agent accepted by EAU Guidelines in 2015 and 2016 to prevent UTI.

Cranberry was used for long time as a fruit, spice or as a treatment, both as juice or dry extract (tablets). There is a long list of ingredients in cranberries: Vitamin C, antocianyde, phlavonooizi, organic acids, triterpens, and catechines. The main component and the most useful is the type A proantocianidin for its effect of antiadesion of *E.coli* to the bladder mucosa.

In this project we divided the number of patients with double J stents into 3 groups:
- group A - Uriactiv litho;
- group B - Cranberry extract;
- group C - Diuretic tea.

We will search the possible benefights of these 2 drugs compared with the classic diuretic plants under different aspects:
- prevention the biofilm and the incrustation;
- acute reflux pyelonephritis;
- UTI.

At the same time, on periodic visits at 30 days we will make a clinical and bacteriological evaluation also a questionnaire asking the patients their tolerance to the double J stents, encouraging the patients to keep the diet adapted to their clinical situation.
and at the same time, to notice the signs of an eventualy „double J syndrome” which will permit us to understand the selfdetermined liquid restrictions; we know our daily practice that the patients who do not tolerate the stents so easily consume a small amount of liquids, to avoid painful micturition, and this fact has important consequences for the stone incrustation.

If the main goals are to identify among these, 2 variants, which can prevent better the incrustation, there will also be secondary objectives:

- The correlation between the grade of tolerance of the stent (a JJ score), the water consumation and the incrustation;
- The profile of the high risk patients that will develop biofilm on the stent or incrustation.

The inclusion criteria will be:
- patients over 18 years old;
- patients with a negative urine culture before stent insertion, no matter the reason for stent insertion;
- patients with a stent for at least 3 month;
- patients who will demonstrate at the end of the month that they took the recommended pills;
- patients who will come regularly at the end of the month with the questionnaire given 30 days prior containing the daily amount of water consumed, the way they tolerate the stent and the medication.

This project is viable for several reasons:
- there are a lot of patients with the profile we are looking for;
- there are a lot of patients at whom, when we extract the double J stent we notice all kind of incrustations on one or both loops, without having a good explanation for that complication;
- there is no clear strategy, generally accepted to prevent the biofilm formation on those stents;

Generally speaking, the patients with a “JJ” stent for a long period of time are more cooperative.

The beneficiaries of this project will be the patients, because they will have a special occasion to be monitored by a regular programme and they will receive advices all along the way. Discovering that a stent have incrustations earlier than expected, will offer the possibility to extract the stent in time, with no major complications or incidents.

Benefits from our study will also have the academic community because we will note precisely our observations and, perhaps, we will identify a strategy more efficient to prevent the stone incrustation.

If we discover a better solution to prevent the stent incrustation, we will recommend our society a protocol which hopefully will be followed by all the urologists in our country, in order to save money and offer a better quality of life to these patients.
III.2.2. STUDIES ABOUT URINARY TRACT INFECTIONS

Another project that we are starting is focused on the urinary tract infections (UTI) problems.
I want to start by presenting an important programme of research from the realities of our country and across the world:

- Romania is on the second place in Europe at the use of antibiotics;
- Every day it is estimated that more than 600,000 persons receive and take antibiotics;
- One of the most spread infection is the UTI;
- An alarming rising of the multi drug resistance (MDR-UTI) was announced in recent studies and the danger that one day, not far from today, we will be in the situation of not having an available antibiotic drug active in vitro against the resistant bacteria;
- For economical reasons there is a lock of funds regarding strict hygienic measures (materials and personel) in the public space and more dangerously in the bureaucratic one and this fact, the lack of investment it is thought to be compensated by using the latest generation drugs. This policy will have a desastruos consequence in the future, because anyone can see that the rhythm of the pharmaceutical companies discovering new molecules in order to fight new resistant germs is far too small comparing the rhythm the germs evolve.

We know, from the study we have made in our departament in the recent years about MDR-UTI that it represents a delicate and severe problem we have to face: during a 16 month period in our department 2944 patients were admitted out of which 750 had developed UTI out of which 336 patients were diagnosed with MDR-UTI (44,8% of the total UTI!!!).

The presence in the hospital ward of a patient with MDR-UTI is a problem with numerous impacts:

- The patient himself is a potential source of infections for the medical staff (doctors, nurses, students) and for the members of the families who come to visit them for moral support.;
- The antibiotics used in such cases are expensive and, even after the acute phase has gone, the patient will stay longer in the hospital and the costs will be higher.
- There is no programme to inform and educate the patient with such an agressive infection about the consequences of his pathology (many of them have associated pathologies such as prostatic tumors, renal tumors, bladder tumors, stones, etc.) which complicate the situation, the evolution and the long term survival.
- After the pacient leaves the hospital, there is no organised system to monitor the evolution, other treatments, etc., so we do not have a database to draw conclusions about the efficiency of the treatments.

We will include in this study all the patients with UTI and MDR-UTI and we will follow the treatment, the evolution, the recurrence, the side effects, reporting the other antimicrobial treatments before the admission in our departament. We want to see if there is a connection between other infections (ORL, respiratoty, etc.) which had determined other doctors to administrate antibiotics and to star the discussions about the strategies for empiric treatment considering the risk of prescribing drugs that are
already resistant for a large category of UTI.

The experience accumulated in this study will be at the beginning of a long and serious dialogue with other colleagues from the region in order to avoid, for a period of time, the recommendation of several very utilised antibiotics nowadays. The goal is to stop using them for a reasonable period of time so that the germs could recover the sensibility for Ciprofloxacin and other drugs overused in the present time.

We have a good experience with the drugs highly recommended by the doctors in the late 90’s and abandoned because of their resistance. These days, for many people, these drugs are the only solution on the in vitro antibiogram. (e.g. Sulfametoxazol with Trimetoprin, better known as Biseptol or Nitrofurantoin, Negram, etc.).

It is clear that this list of banned overused antibiotics should be discussed firstly with all the specialists from the infectious disease department and other doctors who frequently use the antimicrobial drugs. After a serious debate, the list will represent a guide in their and our activity. We have the experience of the cases of infected hydronephrosis over the costs of treating the patients on the empiric bases. Using the drugs for patients with fever and lumbar pain, regardless their past and their possible UTI is the shortest way to change the clinical picture of the case and delay the right diagnosis or the ideal treatment. We must avoid to prescribe in such cases antibiotics based on the prospect of the antibiotic rather than the reality in the regional hospitals. So, only a direct and sincere discussion about the realities we face these days in the field of UTI can improve our success rate of these patients with a serious condition.

I do not have the illusion of an easy task, I presume that many people won’t be willing to change their “habits” of empirical drug prescription, but if we do not learn from the past, we will not have any excuse for the next generations.

I have the intention to follow the patients with the so called “simple UTI” or uncomplicated UTI because these infections have a high recurrence rate most often determined by incompletely treated urologic pathologies, such as kidney stones, with residual fragments, prostate tumors, etc. In all these cases, a simple UTI can be transformed in a MDR-UTI with the possible evolution mentioned above.

Patients included in this study will be over 18 years old, admitted after a confirmation of a the UTI.

We will monitor:
- hygienic conditions at home (running water, toilet, bathroom);
- personal infectious disease record and treatments;
- the antibiotics taken in the last year (period, type, dose, reasons) other than urological infections;
- urological comorbidities (kidney stones, congenital malformations, prostate tumors);
- medical comorbidities (diabetes, constipation, etc.);
- urological interventions or maneuvers in the last 12 months;
- other interventions such as surgical, gynecological, etc. and the antibioprophilaxis taken before;
- urine culture file in the last 12 month (do we notice changes in the sensibility of germs?);
- the period of admission in the hospital (are there any corelations for certain periods of the year / same germs?);
- can we identify in the same hospital ward, at the same time, an identical antibiogram for the same type of germs? In what context?;
- is it a patient with a permanent foley catheter? In what context?;
- is it a patient with a double J stent? In what context?;
- what are the antibiotics (dose, period) received in our department? What was the evolution under those circumstances?;
- how is the situation at the periodic control?.

All these precious informations will be preserved in a special dosier of the patient, a dosier that can be reached very easily if any recurrence occurs.

The main goals of the study will be the identification of the antibiotics that should be, in the specific context of our regional hospitals, temporary abandoned from the daily use as an empirical recommendation in several infections and to design a strategy for the future MDR-UTI challenges. In other words, a plan based on the realities of our daily practice in order to avoid the MDR-UTI in the future or, at least, to limit their impact.

A secondary goal will be the identification of the factors that can explain the occurrence of difficult to treat infections and the measures to be taken to limit the spread into the community.

All of my research projects will be done in “Dr.C.I.Parhon” Clinic Hospital under the supervision of University of Medicine and Pharmacy “Grigore T. Popa” Iasi with the help of my colleagues from Nephrology and Infectious Disease Department. I am convinced that the young specialists and PhD candidates will have many interesting things to research beyond these 2 major projects, offering the academic community an original and useful PhD thesis.
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