"OVIDIUS" UNIVERSITY FROM CONSTANȚA

DOCTORAL SCHOOL OF MEDICINE

FIELD OF MEDICINE PhD

CONTRIBUTIONS ON MEDICAL TREATMENT OF BENIGN PROSTATIC HYPERTROPHY

ABSTRACT

DOCTORAL THESIS

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Content

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Introduction

In the Egyptian papyruses, appeared 1500 years before Christ, is mentioned the benign prostatic hypertrophy as a primary cause of male voiding disturbances, being recognized 1000 years later by the who was the father of medicine, Hippocrates. This affection represents the most frequent benign tumor found in elderly men and creating a high degree of discomfort affecting the patient's normal activity. Benign prostatic hypertrophy has become a major global health problem both in its frequency by which it determines the complications and the problems of diagnosis and treatment it requires.
BPH is a heterogeneous disease. The symptoms attributed to BPH may have other coexisting causes and growth factors both androgen-dependent and independent, which promotes prostate enlargement. It is well known that prostate size correlates poorly with the symptoms so that reducing prostate using 5-alphareductase or alphablocants inhibitors may not always be sufficient. A better understanding of the pathophysiology of BPH and its interactions with other drugs will help the development of new substances with a better efficiency.

The causes of BPH are not well known, but it is recognized the important role played by androgens. BPH is the most common benign tumor of men starting from the age of 50-60 years. The prevalence of disease increases from 8% at men aged 30-40 years to 50% at men aged 50-60 years old and more than 80% at men over 80 years of age.
This present work aims to be a modest contribution related to medical treatment in benign prostatic hyperplasia and the role that the GP should play in managing of this urinary disease quite common in elderly men.

Abbreviations used in text

AMP – adenosinemonophosphate

ATP – adenosinetriphosphate

AUA – American Urological Association

bFGF – fibroblast growth factor

DHT – dihydrotestosterone

EGF – epithelial growth factor

HBP (BPH) – benign prostatic hypertrophy

KGF – keratinocyte growth factor

LUTS – lower urological tract symptoms

PSA – prostate specific antigen

PSAD – prostate specific antigen density

PSAV – Prostate specific antigen velo**c**ity

RAU – acute urinary retention

RCU – chronic urinary retention

RS – simple renal scan

SISP (IPSS) – International Prostate Symptom Score

TGF – tumoral growth factor

TUIP – transurethral incision of the prostate

TUR-P – transurethral resection of the prostate

UIV – intravenous urography

UOI – internal optical urethrotomy

PART I

CURRENT STATE OF KNOWLEDGE REGARDING BENIGN PROSTATIC HYPERTROPHY CLINICAL AND THERAPEUTICAL INTEGRATION

Benign Prostatic Hyperplasia

II.1. The etiology of benign prostatic hyperplasia

In benign prostatic hypertrophy they are incriminated a multitude ways of producing. These has formed a multi factorial causes. There is currently no viable evidence that smoking, vasectomy or obesity, and alcohol consumption would be risk factors in the formation of this disease.

Chronic conditions like high blood pressure or diabetes type were made in connection with benign prostatic hypertrophy, but with their increased frequency in older men, a large proportion of cases are the associations between these disorders. The only factors involved in the disease are certainly age and hormonal status. These issues regarding benign tumor development due to hormones are known more than 100 years. At present it has been deepened studies in molecular biology, certifying and attesting these theories. Benign prostatic hypertrophy is a disease closely related to the aging process and thus the decrease of hormonal secretion of the adult normal sexually able. By the appearance of benign prostatic hypertrophy is confirmed certify of symptoms of lower urinary floor (LUTS) in elderly men. Currently LUTS symptoms is related to the phenomenon of atrophy and aging bladder detrusor muscle. In addition, urinary obstruction in benign prostatic hypertrophy may result in a wide variety of neurological symptoms in the urinary bladder who also contributes at the symptomatology train.

From the histopathological point of view, benign prostatic hypertrophy is characterized by an increase of epithelial cells and the stromal cells in the periurethral region of the prostate. Until now, the development of the individual human prostate glands do not grow than in the fetal period. These truths in the evolution of man's body has given rise to a concept of embryonic development of prostatic stromal cell inductive potential. Increased number of cells may be a result of the proliferation of epithelial and/or stromal or a programmed cell death (apoptosis) of cells deficient in various components of metabolic activities which may lead to cellular accumulation deficient counterparts. Androgens, estrogens, the interaction between stroma and

epithelium growth factors plays a role, either individually or in combination in the process of forming the etiology of BPH.

II.3. The pathophysiology of of benign prostatic hypertrophy

Benign prostatic hyperplasia starts in the periurethral transitional zone of the prostate by the appearance of some nodules that develop and push peripheral prostatic tissue, resulting a pseudocapsule, "surgical capsule".

A particular feature of human prostate is the presence of prostate capsule wich plays an important role in the development of lower urinary tract symptoms (LUTS) by transmitting the pressure to the urethra, thereby increasing urethral resistance.

The effects of obstruction on the bladder and upper urinary tract

The bladder response to obstruction is an adaptive one. Many of the symptoms of prostatism are correlated with changes in bladder function (approximately one third of patients continue to have voiding dysfunction and postoperative).

Obstruction induced changes are of two types:

- changes which causes detrusor instability or decreased compliance - associated with clinical symptoms of urinary frequency and imperiousity
- changes associated with decreased detrusor contractility - clinically associated with decreased strength of the urine stream, jet discontinued, increased residual volume, etc., which may lead to detrusor insufficiency. Acute urinary retention but should not be seen as an inevitable result of this process, many patients having a good detrusor function.

Initially, the bladder detrusor performed a compensatory hypertrophy wich tends to overcome urethral resistance. There is a thickening of the bladder wall which over a period of time manage to overcome the intensity of urethral obstacle. Persistence obstacle determine:

- detrusor instability, frequent cause of micturition urgency

- trabecular wall bladder (cystoscopy aspect "fighting bladder with cells and columns").

- occurrence of bladder residue

- occurrence of bladder diverticula

Residue bladder and bladder diverticula are factors favoring infection, bladder stones and bladder squamous cell carcinoma.

The effects on the upper urinary tract:

Initially, it determines ureterohydro bilateral nephrosis (obstructive uropathy) which ultimately leads to degeneration of renal function and the occurrence of chronic renal failure by progressive atrophy of the renal parenchyma (obstructive nephropathy).

This stasis at the level of upper urinary tract occurs through several mechanisms:

- increasing the intravesical pressure and bladder residue at each micturition preventing draining the ureters.
- losing valvular mechanism of uretero vesical junction with vesicoureteral reflux during micturition act.
- relative ureteral obstruction performed to the bladder wall hypertrophied.

If the obstruction cause is the prostatic hypertrophy is also added a mechanism - Snap – of ureters "in the fish hook" at crossing with deferent ducts, thus making ureteral obstruction:

- impairment of uretero-vesical junction with bladder rectovesical reflux;
- hydro uretero nephrosis with renal parenchymal destruction;
- urinary stasis and infection supra;
- renal insufficiency.

Urethro bladder obstacle repercussions:

- muscle hypertrophy and hyperplasy causes fighting bladder;
- bladder diverticula;
- bladder residual < 300 ml;
- incomplete retention of urine with bladder distention > 300 ml;

- complete urine retention with bladder globe;
- bladder stones;
- urinary infection.

II.5. The clinical diagnosis

Clinical symptomatology

Prostate adenoma involves each individual variable clinical signs. Majority of patients mistakenly think, considering that once aging phenomenon is normal not to pee like at 20 years.

This explains why the first clinical consultation is very different. For easier understanding I will present standard disease in three phases of evolution:

1. The beginning phase marked by the appearance of the following disturbances, called voiding lower urinary tract symptoms **(LUTS)**:

- pollakiuria (frequent urinating) essentially nocturnal onset, particularly in the 2nd half of the night. It can become very intense and troublesome. It is not considered pathognomonic sign, it could be found in other disorders of the lower urinary.
- dysuria (difficult micturition) is less common than urinary frequency and occurs delayed, with the following characteristics:
    - the micturition starts hesitant
    - the jet is poorly designed and flows slowly forcing all the time to exercise the patient's abdominal effort.
    - The micturition is intermittent, it takes long (over 15-17 seconds) ending abruptly, but drops disagreeable "in the manner of a water tap with broken seals." Dysuria worsens whenever the patient can not urinate on time.
- Other symptoms with associated character:
    - nocturnal erections intense and painful urination soothed.
    - tightness pelvic pain.
    - painful ejaculation.

The pain, non characterizing the presence of adenomas when it is too intense, it force us to think of associated pathology (especially prostatic lithiasis).

The symptoms are exacerbated by the following circumstances:

- sedentary life that emphasizes pelvic venous stasis.
- overeating (spices, alcohol, etc.).
- long journeys by car.
- prolonged retention of urine between two micturition.
- diuretics.
- administration of parasympathicomimetic wich can paralyze the bladder.

2. Incomplete chronic retention phase of urine without bladder distention

The transition from the first phase to incomplete retention chronic phase of urine is slow marked by progressively increasing difficulty voiding. Pollakiuria can become so intense nocturnal and diurnal. We can associate:

- voiding imperiosity,
- pelvic and perirenal pressing.

This phase is characterized by a post-micturition residue to the functional capacity of the bladder (approx. 300 ml). This residue may be clinical evidence (bimanual palpation: index rectal right and left hand pressing and percussion hypogastric hypogastric) or ultrasound. No residue permissible determination postmicţional rectovesical bladder catheter considered today as potentially infective therapeutic maneuver iatrogenic.

If the patient is indicating urography examination also, post-micturition residue will be appreciated on the radiographic postmictional cliché centered pelvic.

Histologically, the bladder wall hypertrophy and hyperplasia is characterized by smooth muscle cells that become more numerous. Simultaneously increase the amount of intramuscular connective tissue, collagen fibers but not so with sclerosis and fibrosis. After several months (maximum 6 months) from adenomectomy, these histological changes are submitted, the bladder wall becomes histologically normal. The bladder muscle hypertrophy generate endo-bladder appearance of cells and columns - bladder "battle" (the columns muscle hypertrophy plexiform bundles and cells, areas of bladder

mucosa "depressed" located between the bundles. In the extreme, the bladder will appear single or multiple bladder diverticulum.

3. Incomplete chronic phase retention of urine with bladder distention

In this phase, the residue postmictional than normal functional bladder capacity (approx. 300 ml) causing permanent distension of the bladder, usually clinically manifested by urinary incontinence "by too full" original nature nocturnal and diurnal then. Usually associated with urinary frequency and dysuria intense. Urinary incontinence as "too full" can sometimes occur if post-micturition residue is much higher, the patient situation to accuse only pollakiuria and dysuria.

Chronic retention of urine incomplete bladder distension keeping spontaneous urination even if abnormal, creates a dangerous condition for the patient, which allocates only age quality of micturition, because over a long time can pass to the next stage called phase bladder distension. Now you can install and vesico-renal reflux. At this stage not only the bladder is distended, and the entire upper urinary tree, thus causing after an obstructive chronic renal failure. Clinical syndrome of uremia plus urinary symptoms before, thirst and polyuria are the two main signs. After a while the renal insufficiency may be reversible only partially effective despite a urinary drainage provided.

Histologically, Chronic retention with bladder distention and/or urine is marked by occurrence of irreversible changes in collagen tissue represented more richly represented. Hypertrophied muscle fibers are gradually dissociated from the collagen tissue, preventing normal transmission of nervous influx board neuromuscular inducing abnormal muscle contraction due to distance neuromuscular contacts, thereby reducing parasympathetic innervation. The bladder becomes so not only relaxed, but hypotonic or atonic elements that por-cisto be identified by manometry. This condition is preceded by lower bladder compliance with the emergence of involuntary contractions of the bladder during filling, 70% of patients.

A significant proportion of these patients can not urinate spontaneously after adenomectomy (classical or TUR-P), for which insurance rectovesical bladder drainage

for 2-4 weeks is recommended, either pre-operatively or post-operatively . This case likely to be well known both urologist and patient.

4. Full Chronic retention of urine is a rare condition that is chronic incomplete retention of urine or urinary bladder distension, urinary us as possible.

Sometimes those with Chronic incomplete retention of urine with or without distention or urinary bladder may occur by accident evolutionary emergence of complications are:

• Hematuria often induced by the presence of large median lobe developed endovezical. You have to stick with the idea that no hematuria characterized prostate adenoma, but when there may be initial total rarely even terminal. Putting to rest of bladder probe rectovesical bladder usually leads to remission of hematuria. Treatment with Proscar (5-α reductase inhibitor) greatly reducing vascular proliferation and epithelial factors, has good effect on BPH hematuria date

• Infection is common as an adenoma, the gland volume increases suddenly very painful. Clinical takes the form of a fever or acute cystitis, or in the form of an acute urinary retention. Drainage in this last condition will ensure only the supra-pubic cystostomy "a minimum" percutaneous performed with local anesthesia urgency. Acute epididymitis may occur after adenoma rarely totally asymptomatic. Sepsis can occur after adenoma, especially if drainage is acute urinary retention, bladder urethro probe.

• bladder lithiasis secondary to stasis is a well known complication form single or multiple radio-opaque or transparent depending radio-chemical composition of gallstones. Occurring disorders are more pronounced voiding or post-micturition micturition pain with irradiation glans penis, usually associated with hematuria total. Clinical pain settles at night (at rest) and emphasizes the day, when the patient moves having so provocative. Very often the patient perceives its calculation bladder movements due to body movements. Causing bladder irritation persists, post-micturition residue can be "false" when reduced adenoma complicated with lithiasis. Also, stones exert chronic irritation may induce bladder glandular or epidermoid metaplasia of glandular cancers which can develop bladder (bladder adenocarcinoma) or squamous cell carcinoma of the bladder (epidemoid). Sometimes bladder carcinoma

is associated with an adenoma type urothelial this reason. Carcinomas developed bladder diverticula diverticula secondary prognosis as having muscular layer, mucosal tumor jump from stage (Ta) perivesical stage (T3b - T4). Diverticulum developed bladder cancer diagnosis is difficult.

5. Acute urinary retention may inaugurate history of prostate adenoma (in 10-15% of cases). Sometimes we find acute urinary retention secondary to an adenoma above. Acute retention of urine inaugural can be triggered by:

- spicy foods.
- alcohol.
- state of nervous stress.
- Stay on a cold object.

All these factors increase the tone of alpha receptors in muscle cells that enter into the constitution of adenoma increasing the dynamic obstructive component (functional) suddenly.

Giving a central role in the symptoms of benign prostatic hypertrophy is important to have tools to assess these symptoms and to follow patients over time to determine both disease progression and appropriate treatment.

Over time there have been several attempts to get a tool to assess the situation prostatic symptoms. Test only materialized and was accepted by the international urological community was AUA score (American Urological Association). AUA score was approved by an international group of experts and internationally, this test is called Prostate Symptom Score International (IPSS). This score is a feature that can be used to measure the patient and the severity of the symptoms of the patients groups of 3 types of symptoms: mild (score 0-7), moderate (score 8-19), and severe (score 20-35).

What is the address of the therapeutic point of view of a patient with BPH in the prostate depending on the severity of the symptoms?

Patients with mild symptoms (IPSS 0-7) require no treatment (watchful waiting). Patients with moderate symptoms (IPSS 8-19), we can offer several alternatives: watchful waiting, medication, or surgery, depending on objectives and laboratory investigations. For patients with severe symptoms (IPSS > 20) we choose

between the medical or surgical treatment depending on the presence or absence of complications.

Clinical examination

- Digital rectal examination is associated with hypogastric palpation main examination. The patient is best placed in the supine position with hips flexed supporting leg couch consultation on the heel. Index examiner's right hand is introduced gradually through the anal canal rectal ampulla and press the left hand immediately over-pubic hypogastric. Identifies a finger rectal swelling exhibited more or less normal median transverse groove disappeared.
- Enlarged prostate without induration is firm but elastic, homogeneous, partially mobile and painless, has smooth surface is well defined, with median groove preserved. Clinical examination difficulties in obese people because of the thickness sharp perineum.
- Digital rectal examination may reveal conditions associated anorectal fissures, fistulas, internal and external hemorrhoids, tumors of the anus and rectum.
- Pair of prostate (adenoma) can create irregular appearance to DRE may be fluctuant or compression can cause the patient pain. The differential diagnosis will be made and prostate cancer by histological examination of the specimen taken by puncture biopsy of the prostate, transrectal or transperineal ultrasound-guided by endo-rectal transducer.
- This mode will allow examination and collection of post-micturition residue, especially if it is followed by percussion hypogastric. It will feel and septic back to detect a large kidney became palpable suffering from hydronephrosis secondary of urethral obstruction adenomatous.
- A large globe chronic bladder may induce swelling of the lower limbs compression exerted on the femoral veins, swelling that will resolve after the establishment of effective bladder drainage.
- Do not forget that because of dysuria may be associated unilateral or bilateral inguinal hernia various clinical anatomical forms.

- Clinical examination will be conducted at testicles and epididymis to identify a possible epididymitis or consecutive orhi epididymitis, an adenoma. Adenoma volume can be assessed only by clinical examination all about.
- By rectal we can see the appearance of prostate adenoma pathological differentiate from other diseases:
- - Adenocarcinoma of the prostate;
- - Acute prostatitis;
- - Bladder lithiasis (computing inclavat the bladder neck);
- - Year bladder tumor developed bladder neck, A
- - Urethral strictures;
- - Urethral calculi;
- - Urethral tumor;
- - Urethral meatus stenosis;
- - Phimosis and Paraphimosis;
- - Neurological bladder;
- - Urethral or bladder foreign bodies.

Micturition calendar

The calendars (journals) voiding are simple to complete and can provide useful clinical information and objectives. Currently not available a frequency-volume chart type standard. Recent data show that a 24-hour micturition diary is sufficient, and longer periods of time only offer little additional information. Voiding diaries allow the identification of patients with nocturnal polyuria, one of the causes of urinary frequency in elderly men.

Quality of life index

Quality of life according to urinary symptoms	Pleased	Satisfied	More than satisfactory	Equally satisfied and dissatisfied	More dissatisfied	Infelicitous	Appalling
If you were to spend the rest of life in the current situation	0	1	2	3	4	5	6

Total score QoL

Scores to assess severity of prostate adenoma

Evaluation of IPSS (International Prostate Symptom Score)

Symptoms score	Not at all	Less than once per day	Less than half from time	Approxi mately half from time	More than half from time	Almost always
In the last month how often have you had the feeling that you have not completely emptied your bladder after you finished urinating?	0	1	2	3	4	5
In the last month how often you had to urinate again less than 2 hours after the last urination?	0	1	2	3	4	5
In the last month how often it happened that, while urine stream to stop and then to resume?	0	1	2	3	4	5
In the last month how often did you find it difficult to postpone the urination?	0	1	2	3	4	5
In the last month how often have	0	1	2	3	4	5

you had a weak urinary stream?						
In the last month how often had to push or force start urination?	0	1	2	3	4	5
In the last month how often you wake up to urinate at night?	0	1	2	3	4	5

The differential diagnosis of prostate adenoma

- Adenocarcinoma of the prostate;
- Acute prostatitis;
- Bladder lithiasis (computing inclavat the bladder neck);
- Year bladder tumor developed bladder neck, A
- Urethral strictures;
- Urethral calculi;
- Urethral tumor;
- Urethral meatus stenosis;
- Phimosis and Paraphimosis;
- Neurological bladder;
- Urethral or bladder foreign bodies.

Benign prostatic hyperplasia treatment:

- Hygienic-dietary;
- medical:
    - phytotherapy
    - alpha-blockers
    - 5α reductase inhibitors
    - combination of alpha-blockers and 5α reductase inhibitors;
- minimally invasive:
    - transuretral neadle ablation - TUNA
    - transuretral microinasive thermo-therapy - TUMT
    - laser therapy
    - cryotherapy
    - intraprostaticstents;
- surgically:

- open:
    - transvezical
    - retropubic
    - perineal
- endoscopic - TURP.

PART II

PERSONAL CONTRIBUTIONS ON THE KNOWLEDGES DEVELOPMENT OF BENIGN PROSTATIC HYPERTROPHY

Tasks

Clinical research in this study is mainly aimed at studying the effectiveness of non invasive treatment of prostate adenoma were used as methods of therapy drug therapy (alpha-blockers, 5a-reductase inhibitors, combination therapy) and active surveillance of patients suffering from this condition. For efficiency and purposefulness main monitor and set the weight of each type of non-invasive treatment and medication, performing correlations between patient age and the treatment used. Also analyzed the effects or side effects of medical treatments applied.

It attempts to identify prognostic factors according to the applied therapy, outlining an algorithm for noninvasive treatment of prostate adenoma and conduct of medical and professional factors based on collaboration between urologist and specialist physicians. These considerations are based on male patient suffering from the disease of old age, the ultimate goal being to improve clinical symptoms easing the natural evolution of the disease and the patient's social integration.

Chapter IV
Material and method

Clinical research conducted in this study has as main purpose the effectiveness of medical treatment with alpha-blockers, 5-alpha-reductase and their combined therapy. I aimed to establish the proportion of each type of non-invasive or medical treatment and studied the correlation between age and the treatments used. I studied the side effects of drugs, identification of prognostic factors and the failure of medical treatment.

In the end I outlined an algorithm for non-invasive treatment and made a proposal to optimize collaboration, family physician urologist in evaluating patients with LUTS suggestive of BPH in patients candidate to undergo treatment nonivaziv. I made up a patient guide.

I performed a retrospective and prospective on a lot size of 384 patients aged between 50 and 87 years, prostate adenoma, treated non-invasive or medical treatment or by active surveillance (watchfull waiting). Diagnosis of prostate adenoma or benign prostatic hyperplasia was established within the Cabinet of Urology - Professor PhD. Viorel Tode Constanta Romania (202 patients) and the Cabinet of Athens Eye Hospital Polyclinic Urology - Athens, Greece (182 patients). Patients were monitored in the cabinets above and in the office of primary care - family, diagnostician collaboration between specialist urologist and general practitioner, family.

The study was conducted between January 2009 - June 2013, during this time period being monitored both patients already in treatment and newly diagnosed patients.

It have been established criteria of inclusion/exclusion in the study, the essential criteria in smooth pursuit in patients treated medically. In this sense, the study excluded patients with a history of proliferation/tumor urothelium of patients with neurogenic bladder patients with diabetes and patients with surgery or lower urinary tract diagnosed with malignant tumors. Fixing these exclusion criteria is due to the influence

of the conditions listed drug and combination therapeutic effects of the underlying disease treatment effects of prostate adenoma.

Most patients studied have been shown to lower urinary tract symptomatology (LUTS) - 325 cases, the remaining patients are presenting with complications of prostate adenoma: acute urinary retention - 12 cases, hematuria - 8 cases, infectious complications - 39 cases, including cystitis, acute/chronic - 17 cases, acute prostatitis - 12 cases, acute orhi epididymitis / acute epididymitis - 10 cases.

The diagnostic protocol included A minimum of clinical and laboratory investigations useful in precise determination of the form of the disease. These investigations were represented by:

- Anamnesis
- Clinical examination of the patient associated with urological examination including digital rectal examination
- Determination symptom score using IPSS (score international prostate symptom) to monitor the quality of life
- Determination of prostate specific antigen – PSA
- Assessment of renal function by determining urea and serum creatinine
- Perform urine analysis examination
- Determination of the bladder residue by abdominal ultrasound
- Uroflowmetry to 182 patients from a total of 384 cases (group of greek patients) - uroflowmetry measurements were performed in the Urology Clinic of Athens Eye Hospital - Athens, Greece.

Apart from the above investigations I conducted a series of additional investigations to certain categories of patients such as:

- uroculture for patients with pyuria
- renal ultrasound to patients with creatinine above 1.2 mg/dl, hematuria or pyuria
- simple renal radiography, intravenous urography, cystography or post micturition cystography to patients with hematuria

- ureteritis cystoscopy to patients with hematuria or with suspected urethral strictures.
- micturition Journal, in some cases.

Active surveillance, as non-invasive treatment method was applied to all patients and associated drug therapy and consisted of:

- Measures to amending lifestyle by:
  - reducing fluid intake to decrease urine output at certain times of day (evening/night) without necessarily diminish daily intake of 1500-2000 ml;
  - avoid alcohol, salt, spices;
  - review of cardiac medication with urinary effects (for hypertensive patients - adjustment of the diuretic)
- Monitoring during 6 months and then annually following the same lifestyle changes as well as changes in IPSS (international prostate symptom score)

The medical treatment consists of the administration of:

alpha-blockers

Tamsulosin 0,4mg – 1 tablet/day,

Doxazosin 4mg – 1 tablet/day

Alfuzosin 10 mg – 1 tablet/day

5alpha-reductase inhibitors

Dutasterid 0,5mg – 1 tablet/day

Finasterid 5 mg – 1 tablet/day

combined therapy – alpha blocker and 5alpha-reductase inhibitor

Tamsulosin Dutasterid

Tamsulosin Finasterid

Doxazosin Finasteri

Doxazosin Dutasterid

Alfuzosin Finasterid

Alfuzosin Dutasterid

DUODART

Patients were followed from 6 weeks up 76 months, with an average of 32.9 months and was performed by:

- Anamnesis
- IPSS (International Prostate Symptoms Score) which includes the evaluation of quality of life
- Digital rectal examination
- Ultrasound abdominal pelvine.
- Determination of total serum prostate specific antigen (PSA)
- Assessment of renal function by testing serum creatinine
- The urinalysis examination

  The reevaluation carried out in the following time:
  - Active surveillance - 6 months
  - Patients treated with alpha-blockers - 6 weeks
  - Patients treated with 5-alpha-reductase inhibitors - 6 months, then annually.
  - Patients treated with combined therapy - 6 months, then annually.

For patients were drawn individual sheets which included consultations registry data as well as clinical and laboratory modified elements. Individual form containing the following particulars patient:

- Data individual identification: name, date of birth, address and profession
- Age at the moment of diagnosis - study entry
- Personal pathological antecedents and heredocollateral
- Grounds for presentation - symptoms of disease onset:
  - Lower urinary tract symptoms
  - Complications:
    - Infections: cystitis, prostatitis, orhi epididymitis / epididymitis
    - Hematuria
    - Acute retention of urine

- IPSS (International Prostate Symptoms Score) using the questionnaire required by the European Association of Urology
- Prostate volume (determined by echography and measured in cm^3)
- Bladder residue (determined by echography and measured in cm^3)
- Maximum urinary flow
- The level of serum total PSA (ng/ml)
- Emergent adverse effects during therapy
- Recurrent reappearance of complications (infections, hematuria, acute urinary retention)

- The elements contained in the individual patient tracking sheet used to make the following findings:
- • Age analysis of the occurrence of symptoms of disease onset
- • Analyze how the onset of the disease
- • Distribution of cases by year of study
- • The correlations between age and type of treatment applied
- • The role of IPSS (International Prostate Symptoms Score) in choosing non-invasive treatment modality
- • Assessment of the effectiveness of the alpha-blocker chosen (Tamsulosin) the satisfaction of the patient, the degree of improvement in IPSS, maximum urinary flow rate increased
- • Assessment of the effectiveness of 5a-reductase inhibitor (dutasteride) in satisfaction of the patient, the degree of improvement in IPSS, maximum urinary flow rate increased, decreased prostate volume
- • Assessment of the effectiveness of combination therapy - are blocker and inhibitor of 5a-reductase (Duodart) the satisfaction of the patient, the degree of improvement in IPSS, maximum urinary flow rate increased, decreased prostate volume

- • Assessment of the effectiveness of medical therapy in secondary prevention of complications associated with prostate hypertrophy - the rate of recurrence of acute urinary retention, hematuria, infectious complications
- • Analyze the side effects

Chapter V
Results and discussions

Ways onset/presentation of patients in the studied group

Lower urinary tract symptoms are not specific only to BPH, they running through a number of other pathological processes similar symptoms. History and physical examination can distinguish them, and further investigations are necessary when the diagnosis is unclear for BPH. Recommendations of the European Association of Urology in 2004, established the explorations that are recommended and even those recommended for the diagnosis of BPH.

Recommended tests are: history, physical examination including digital rectal examination, prostate symptom score international determination of serum prostate specific antigen levels and the levels of serum creatinine, urine analysis exam "meter". Optional exams are studies pressure, flow, uretrocistoscopia, upper urinary tract imaging, imaging of the prostate and bladder, micturition calendar. Examinations are recommended: intravenous urography, filling cystometry, uretrografia retrograde computed tomography, magnetic resonance transrectal.

Taking into account these recommendations, all patients studied were recommended Testing, noting that the meter was performed only in patients diagnosed in Greece.

History was insisting on thorough medical history that interested urogenital: infections, stones, tumors, malformations, etc.., Surgery, and other ailments such as diabetes, neurological diseases, prolonged immobilisation in bed or using drugs

influence the normal function of the bladder. Regarding heredocollateral history if we were interested in were family men with prostate problems.

All patients had undergone a physical examination including digital rectal examination and objective where I thought it needed a neuro consult.

Physical examination I began to examine to emission of urine will reveal the characteristics of micturition act (jet cut, poorly designed, delay in appearance) and evaluation of urine appearance: clear, normochromic or hyperchromic, cloudy, hematuria, pyuria, etc..

Physical examination of the abdomen - inspection, palpation, percussion - to identify a bladder relaxed or inguinal hernias, abdominal tumors, examination of the external genitalia: meatus stenosis, epididymitis, varicocele, hydrocele, testicular tumors, penoscrotal edema.

Digital rectal examination was performed in all patients to evaluate the appearance of the prostate, where BPH witnessed volume, globular, well defined, painless, with median groove deleted elastic firm consistency and uniform unless unique lobe adenoma small, endobladder development. Digital rectal exam helps to detect prostate cancer or other prostate conditions such as acute or chronic prostatitis, prostatic abscess, prostatic stones. DRE can identify and pathological disorders of the rectum, hemorrhoids, fissures, fistulae, abscesses, tumors. Digital rectal exam helps determine prostate volume guiding the treatment that the urologist considers necessary to establish. Digital rectal examination combined with hypogastric palpation may reveal a smaller bladder and flexibility globe bladder walls.

International prostate symptom score. For each patient entered the study was prepared by a table IPSS guidance needed to assess clinical pain, studying and lower urinary tract disorders. The patient self-evaluation points giving 1 to 5 for each of the seven signs or symptoms. They investigated the initial dysuria, decreased size and force urine flow, intermittent urinating and feeling incomplete emptying of the bladder, which are three irritative obstructive symptoms: nocturnal urinary frequency, urinary frequency and imperiozitatea daytime micturition.

Allows the questionnaire score following clasificareŞ

0-7 = mild symptoms

8-19 = moderate symptoms

20-35 = severe symptoms.

I used the score for monitoring progress and assessing the effectiveness of treatment.

To draw sheets I used IPSS patients or giving them chips they have completed individually or helping them to getting answers.

Urine analysis was required and I executed for all patients showing in some cases nitriturie leucocyturia with hematuria due to infections or in combination to BPH urinary stones or tumors. Glucose in diabetes may be the possible cause of lower urinary tract symptoms.

Determination of serum creatinine

BPH causes obstruction underbladder which induce secondary bilateral hydronephrosis and renal failure. Renal impairment usually denotes suffering caused by obstruction underbladder longer, but in some cases delayed diagnosis of prostate adenoma can accompany kidney failure, which requires specific means of health education of the population - increased testing serum creatinine us Orinta diagnosis for upper urinary tract damage and the occurrence of renal failure.

Determination of prostate specific antigen is the most valuable specific marker of prostatic tissue. You do not have any medical treatment recommended before performing a digital rectal and PSA assay. A raised PSA is found in prostate cancer, but sometimes in BPH, prostatitis, acute urinary retention, recent biopsy of the prostate, rectal or after sex, but without clinical significance of PSA. The threshold level is set to 4 ng/ml, but recent studies have decreased to 2.5 ng/ml.

The frequency of false positive results caused by benign prostate disease can be reduced by 20-40% by determining unbound PSA - free PSA. Determination of free PSA has become the practice to increase the specificity of total PSA in diagnosis of prostate cancer when its values are between 4 and 10 ng/ml. If the free PSA is less than 19% of the total PSA, it is estimated that perhaps prostate cancer patient has to be certified by biopsy and histopathology.

Sometimes useful PSA density (PSA Secic / prostate volume > 0,15), PSA velocity (increases greater than or equal to 0,75 mg/ml/year correlated with age - the

serum level increases with age). PSA and the amount of the prostate can be used as parameters of the evaluation of the natural history of benign prostatic hyperplasia, a risk of urinary retention or surgery.

Determination of the bladder residue. Normally at the end of micturition bladder is empty bladder residue is zero. Represents the amount of urine the bladder residue remaining after urination. Can be determined by non-invasive methods - ultrasound and cystography postmicţionale and invasive - postmicţional bladder catheter.

Patients with significant bladder residue we monitored especially if you chose non-surgical therapy, high level indicates progression of BPH and bladder residue are aggressive therapeutic indication especially if it exceeds 100 ml of urine and cloudy.

All patients studied were determined by ultrasound and in some cases postmicţional catheter, bladder residue.

Bladder residue greater than 200 ml bladder dysfunction showed poor results after medical treatment administered.

Uroflowmetria was performed only in the patients group in Athens. Uroflowmetria noninvasive urodynamic test is a test that must be used in the exploration of patients with lower urinary tract voiding disorders. Urinary flow meter is to determine the maximum flow (Qmax) and average flow (Qave) act throughout micturition.

Determination of lower urinary tract obstruction benefit from this investigation is the best non-invasive urodynamic investigation. Q_{max} values below 10 ml/sec indicates a higher probability of obstruction underbladder receiving surgical treatment.

Explorations additional diagnostics

Are represented by the transrectal ultrasound and abdomino pelvine, intravenous urography, computed tomography and magnetic resonance imaging, including transrectal.

Suprapubic and transrectal ultrasonography that provides information important numeorase and measuring the diameter of the prostate (longitudnal, transverse and anteroposterior) from which it can be calculated in cubic centimeters and secondary prostate volume, prostate weight as 1 cc of prostatic tissue corresponds to a gram of

prostate tissue. One can explore the prostate capsule contents existence calcifications, prostatic microabscesses or nodules that can puncture and biopsy.

Ultrasound may reveal bladder stones, diverticula and bladder tumors, intravesical foreign bodies.

Determining the wall thickness of the bladder transabdominal ultrasound can be a non-invasive method for the evaluation of the obstruction subvezicale.

Renal ultrasound may reveal high noise of the obstruction ureterohidronefrozei subvezicale the appearance and even the existence of pathological kidney. Ultrasound is a noninvasive method, low-cost, non-irritating, no side effects and can be repeated as needed. I used it to all cases studied.

Exploring the radiological exploration method is a more restricted indication and well recommended. Renal and bladder simple radiography is made especially when the question arose of underlying conditions: stones, bone metastases, tumors, concomitant hematuria.

Intravenous urography has some characteristic signs of March as incomplete picture based bladder image crescent ureters in fish hook, uretero hydronephrosis, bladder diverticula, bladder residue post micturition etc. Urography is not routine is optional indications in selected cases.

In the study I had only two patients being advised computed tomography or magnetic resonance imaging, including transrectal.

Another investigation can be made in well selected is pressure flow study can staged degree of obstruction and can identify patients with low flow rate due to a weak bladder detrusor contraction. Pressure simultaneous flow used to patients optionally, urging it is before surgery very young or elderly patients, the urine volume of less than 150 mL Qmax, and more than 15ml/sec, the bladder is the residue than 300 ml in neurogenic dysfunction, bladder or pelvic surgery of treatments without success. These investigations were carried out a total of 12 patients Greek.

Uretrocistoscopia investigation is another option which is recommended before surgery or minimally invasive therapies, the treatment depends on the shape and size of

the prostate, men with a history of hematuria, urethral strictures or bladder tumors who underwent surgery of the lower urinary tract .

Uretrocistoscopia show enlargement of the prostate, bladder neck appearance, functional hypertrophy of the muscle of the bladder, the appearance of "cells and columns", of diverticula, the presence of calculi, bladder tumors, bladder residue presence.

Micturition diary is sufficiently prepared for 24 hours, the longer periods giving little additional data. Voiding diaries allow the identification of patients with nocturnal polyuria, nocturnal pollakiuria one of the causes of elderly men.

Most patients treated noninvasively, suffering from prostate adenoma of the study group were presented to the physician with lower urinary tract symptoms (325 cases, 84.64% respectively). A total of 59 cases representing 15.36% of the total study group had complications of BPH: acute urinary retention - 12 cases respectively 3.12%, hematuria - 8 cases respectively 2.08%, infectious complications - 39 cases respectively 10.16% (including cystitis acute/chronic - 17 cases, acute prostatitis - 12 cases, orhi epididymitis acute / acute epididymitis - 10 cases).

Patients with complications	Number of cases	%
Acute urinary retention	12	3,12
Hematuria	8	2,08
Cystitis acute/chronic	17	4,43
Acute prostatitis	12	3,12
Orhi epididymitis / Acute epididymitis	10	2,60
Total	59 cases by 384 total	

Table. No. II. 1. Complications at onset / presentation

It thus appears that in all patients, a percentage of 15.36% have complications that fall within the limit of the application of a noninvasive treatment, respectively surgical treatment.

For these patients I studied the effectiveness of drug therapy in preventing complications of prostate adenoma.

International Prostate Symptom Score role in determining the way noninvasive medical treatment

After the diagnosis of benign prostatic hypertrophy patients studied group, has certified that the patients had absolute indication of surgery, the next step is choosing noninvasive treatment modality. Choosing the type of treatment applied was determined by Prostate Symptom Score International (IPSS). Therefore it was necessary for the patient to understand how exactly the eight questions of the IPSS questionnaire.

Based on the results I divided patients completing IPSS questionnaire into three categories:

- - With mild symptoms - low IPSS 0-7
- - With moderate symptoms – IPSS between 8:19
- - With severe symptoms - IPSS between 20 and 35.

Item no.	IPSS	No. of cases	%
1	Small 0-7	28	7,29%
2	Medium 8-19	248	64,58%
3	Severe 20-35	108	28,12%

Table II. 61. IPSS types identified at patients from the studied group

Treatment with alpha-blockers (Tamsulosin) at studied group patients

It were treated with alpha-blockers the patients with IPSS low and medium prostate volume less than 40 cc and PSA less than 1.4 ng/ml. There were thus included in the study 276 patients, representing a rate of 71.88%. Follow-up period of these

cases ranged from 6 weeks to 76 months, analyzing the short-term efficacy and long-term.

After 6 weeks in 54 of the 276 patients (19.56% of the patients treated with alpha-blockers) have been no changes in the IPSS. Patients whose therapy failed and IPSS at 6 weeks did not change were removed from the study.

Alpha-blockers Short term efficacy	No. of cases	%
Patients with no response to treatment	54	19,56%
Patients who remained in the study	222	80,44%
Total	276	100%

Table II. 62. Assessing the effectiveness of short-term alpha-blockers

Comparative analysis of non-response to therapy with alpha-blockers showed no significant association failures. Nonparametric chi-square test which compared the number of failures reported with alpha-blockers therapy showed a lower correlation coefficient r = 0.2 and a high value level of significance p <0.05, confidence interval being 95%.

Failure versus treatment	chi-square	df	p 95% confidence interval
Maximum probability	0,754410	2	0,88975
Contingency coefficient	0,015763		
Correlation coefficient	0,200511		0,53133

Tabel II. 63. Estimated parameters in testing association therapy with alpha-blockers versus evolution

For those who respond (222 cases), I measured the degree of improvement in the therapeutic efficacy of the IPSS. Overall, Tamsulosin therapy resulted in a rapid improvement in symptoms, IPSS falling short at a rate of 80.44% of patients treated with alpha-blockers, which represents 57.81% of the total group of patients included in the study.

The long-term study efficacy of alpha-blockers included 222 patients with favorable response to short-term assessment. Long-term efficacy was assessed by the lack of alpha-blockers on treatment failure. Failure was defined as the increase in IPSS 12-15 months. Thus, in this study I have lost a total of 71 cases in which the IPSS increases almost as the initial values.

Of the total 276 patients treated with tamsulosin (alpha-blockers) was found efficiency at 183 patients (66.3%), which demonstrates an average efficacy of therapy with alpha-blockers.

Treatment with the 5-alpha-reductase inhibitors (Dutasteride)

Out of the 108 patients with IPSS severe, a number of 33 patients were treated with 5-alpha-reductase inhibitors. The reason for this number of cases was the value of PSA and prostate volume, being included in the dutasteride therapy patients whose PSA value did not exceed 1.4 ng/ml and ultrasound prostate volume exceeded 40 ml.

I analyzed the efficacy of the 5-alpha-reductase inhibitors both short term (6 months) and long term.

I found that for 8 of the 33 patients treated with the 5-alpha-reductase inhibitors, there has been no change ultrasound prostate volume and IPSS values maintained severe, these 8 patients (24.24% of those treated with 5 alpha reductase) were excluded from the study.

At 25 patients (75.76%) remained in the study have undergone evaluation at 12-15 months observing that IPSS improved by reducing rates values between 12 and 18%, demonstrating the effectiveness of treatment with 5-alpha-reductase inhibitors long term, a total of 6.51% of patients in the total group was improved by this treatment.

Treatment with combined therapy (Duodart - tamsulosin 0.4 mg and dutasteride 0.5 mg)

Since January 2003 AUA introduced in patients with severe IPSS, prostate volume 40 cc and higher PSA values of 1.4 ng/ml, combination therapy (5-alpha-reductase associated with alpha-blocker inhibitors). The criteria imposed by ARUA, our group patients were in number of 75 (19.53% of the total lot 384). These patients received combined therapy Duodart form a single tablet containing both alpha-blockers (tamsulosin 0.4 mg) and 5-alpha-reductase inhibitor (dutasteride 0.5 mg). Follow-up period of these patients ranged from 6 months to 24 months, thus assessed the effectiveness of short-term and long-term therapy applied.

After 6 months of combination therapy, for a total of 7 patients out of 75 (at the rate of 9.33%) was observed treatment failure (IPSS has not improved, the life quality of patients being unchanged, demonstrated also by ultrasound).

Favorable response to combination therapy has been shown to decrease prostate volume and IPSS improvements proven ultrasound. In this regard, short-term efficacy was found at a rate of 90.64% of patients with combined therapy (68 patients).

The 68 patients with IPSS improvement in short, remained in the study and were re-conducted long-term 12 to 24 months. Of these 68 cases, a total of 5 cases (7.35%) were found failures terapeurice IPSS worsening or complications (hematuria and infection) leading to surgical indication by TUR-P cases failed .

Of the 75 patients treated with the combination is found by evaluating the therapeutic efficacy both short and long term treatment of the success to a percentage of 84% of cases (63 patients).

Based on the study conducted on 384 patients diagnosed with benign prostatic hyperplasia and on reading the medical literature, I concluded that the issuance of an algorithm for evaluation and treatment of patients with lower urinary tract urinary disorders would be beneficial for physicians family, but also for specialists urologists.

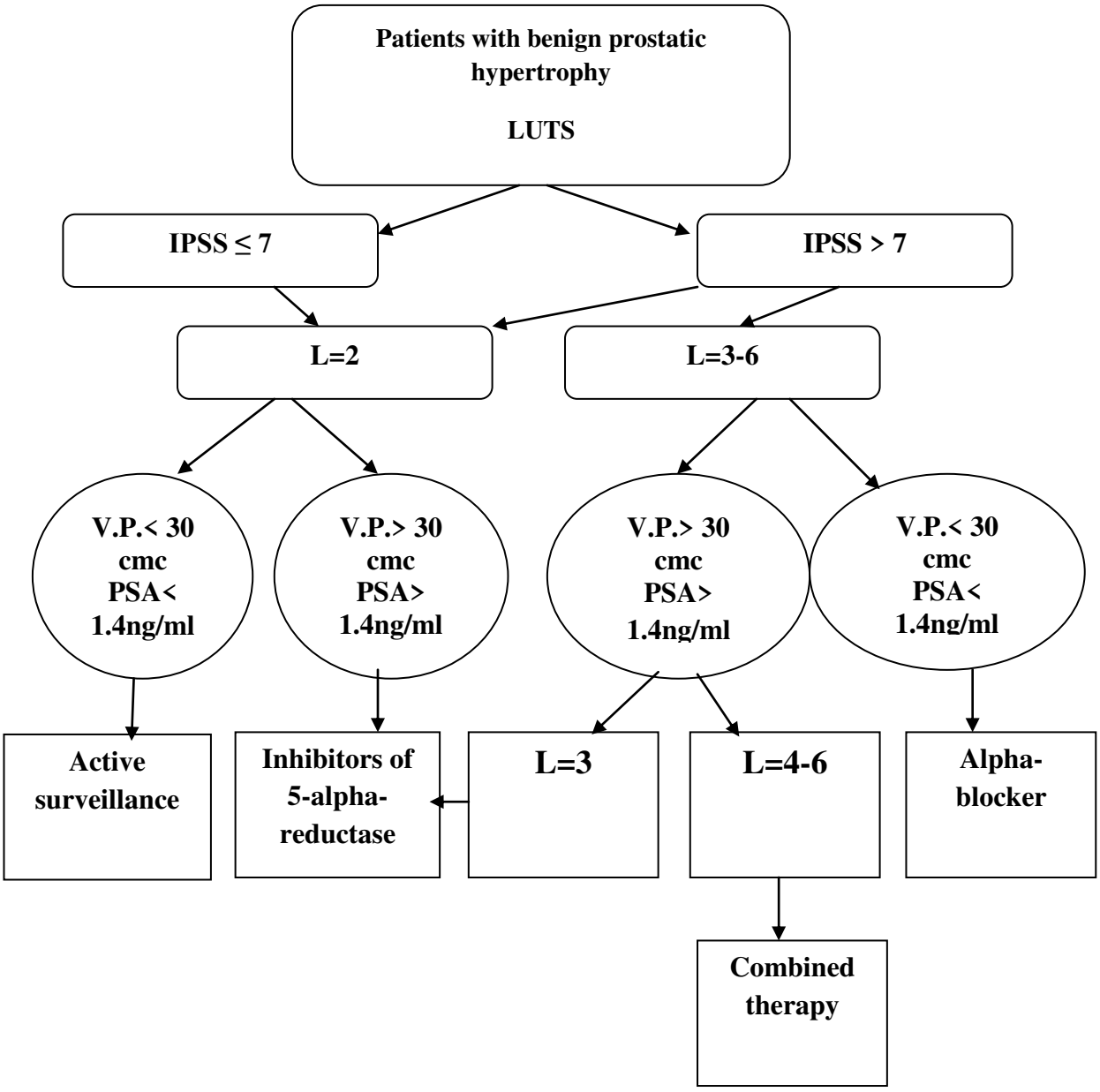

Figure 32. Diagram of the algorithm in the treatment of benign prostatic hypertrophy depending on the patient's clinical presentation. (VP = prostate volume, PSA = prostate-specific antigen, IPSS = prostate symptom score, L = quality of life)

Chapter VII
Conclusions

1. Medical treatment, non-invasive plays an increasingly important role in the therapeutic arsenal indicated in benign prostatic hypertrophy.
2. Active surveillance as the sole means of non-invasive treatment is almost non-existent due to delayed presentation urologist most patients requiring drug therapy.
3. Studied group comprises of 384 patients aged 50 to 87 years, patients were divided into three categories according to the values of IPSS, prostate volume and PSA value.
4. International Prostate Symptom Score (SISP or IPSS) properly prepared is essential in establishing the non-invasive treatment modality.
5. Besides patients with mild symptoms, those with moderate pain may benefit from therapy with alpha-blockers.
6. Alpha-blockers are most commonly applied to medical therapy in patients with benign prostatic hyperplasia. This class of drugs generates a rapid and significant improvement in symptoms, as well as a significant increase in urine flow.
7. 5-alpha-reductase inhibitors causes a substantial reduction in prostate volume, but a more modest improvement in symptoms compared with alpha-blockers.
8. 5-alpha-reductase inhibitors can be used successfully as monotherapy only in patients with severe IPSS, PSA below 1.4 ng/ml, and prostate volume over 40 cc.
9. Combined therapy is superior to the alpha-blockers, and 5-alphareductase inhibitors, both in the short term efficacy, as well as the long term..
10. Of the failure risk factors and medical tratamentlui were found to be severe symptoms of prostate and large. Identifying these factors helps both urologist and patient in choosing the optimal treatment modality.
11. It has been found an efficiency of 66.3% in patients treated with alpha blocker, an efficiency of 75.76% of the cases treated with inhibitor 5-alpha-reductase

inhibitor and an efficiency of 84% for patients treated with combined therapy, where the treatment failure is that the target values have not improved, indicating them the surgical therapy by TUR-P.

12. To establish a rapid drug treatment of patients with symptomatic benign prostatic hyperplasia is necessary to monitor men aged over 50 years by physicians. The family physician must complete IPSS questionnaire with the patient and recommend PSA. Thus, the presentation of the patient to a specialist urologist it to apply to optimal therapy after prostate ultrasound.
13. The role of health education of the population is of great importance in early diagnosis of benign prostatic hypertrophy eligible for active surveillance (watchfull waiting) treatment especially beneficial in most cases uncomplicated. I've compiled a guide to the patient's prostate adenoma proposing to run.
14. Will not ever recommend medical treatment until it will establish the correct diagnosis of any disease of the prostate, the main diagnostic features are: history, IPSS, DRE, PSA, ultrasound examination of urine.
15. The family physician will send to the specialist urologist any man voiding lower urinary tract disorders; urologist will determine the diagnosis and begin treatment; family doctor will give the patient will seek treatment and he will benefit from a periodic review of urology.
16. DRE and PSA tests are routine for every man past 45 years, regardless of condition that to the doctor.
17. In the practical work of the physician he must consider the algorithm that I have set for the use of alpha-blockers, 5-alpha-reductase inhibitors and combination therapy.
18. Ideal for future would be like your family doctor, using protocols evaluation of patients with LUTS, to establish the diagnosis and medical therapy instituted, urologist assuming the only complicated cases that benefit from innovative treatment.
19. I consider that important step towards diagnosis and proper treatment can lead to healing on timely presentation by the patient to the doctor.

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