UAA Consensus on the Management of BPH/Male LUTS (1st Edition)

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Foreword

These Proceedings represent the consensus and recommendation of Benign Prostatic Hyperplasia (BPH)/Male Lower Urinary Tract Symptoms (LUTS) by the 16 countries that met in Pattaya, Thailand at the occasion of the 11th Asian Congress of Urology, on August 22nd 2012, and in Hong Kong on November 10th 2012. On behalf of Urological Association of Asia (UAA), we would like to thank the chairman, the committee members, and Ms. Angie See, Executive Secretary of UAA Central Office.

We also would like to thank JUA, AUA, EAU, and ICUD for kind allowance to use some parts of their Guidelines.

This is the 1st Clinical Guideline published by UAA, hence, is a milestone for UAA.

UAA Representatives
Keong Tatt Foo, Osamu Ogawa, Masayuki Nakagawa
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Preface
1. Purposes of guideline: Practical Consensus Statement on the Management of BPH/Male LUTS
2. Target doctors: Both Urologists and General Practitioners
3. Target patients: 40 years or older male patients with BPH/LUTS
4. Ownership and responsibility of this guideline: UAA

Conflict of interest
All members of the BPH/Male LUTS working group have provided disclosure statements on all relationships that they have and that might be perceived to be a potential source of conflict of interest. This information is kept on file in the Urological Association of Asia Central Office database. These guidelines document was developed with the financial support of the Urological Association of Asia. No external sources of funding and support have been involved. The UAA is a non-profit organization and funding is limited to administrative assistance and travel and meeting expenses. No honorarium or other reimbursements.

Methodology
1. The BPH/Male LUTS Guidelines have been developed by committee members recommended by the Urological Association of Asia (UAA).
2. The members have meticulously reviewed relevant references, retrieved via the PubMed and MEDLINE databases, published between 1966 through Dec 31st, 2011.
3. The search strategy includes the Medical Subject Headings (MeSH) for BPH and LUTS: “Prostatic Hyperplasia”[MeSH] AND Benign; “Urinary tract”[MeSH] AND Symptoms AND Lower. Other key words for searching references will be selected by each committee.
4. Other sources of information include
   1) JUA clinical guidelines for benign prostatic hyperplasia,
   2) The BPH Guidelines 2010 published by The American Urological Association (AUA)
   3) Guidelines on the Treatment of Non-neurogenic Male LUTS2011
      The European Association of Urology (EAU),
   4) The meeting reports of the 6th International Consultation on
New Developments in Prostatic Cancer and Prostatic Diseases.
“MALE LOWER URINARY TRACT DYSFUNCTION; Evaluation and Management”

6. Level of Evidence & Grade of Recommendation for each treatment will be made according to the following strategy. The recommendations of the treatments are based on a non-structured literature search, which has been previously shown, and labeled with a Level of Evidence (LE), according to a classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence*, ranging from LE:1 (highest evidence level) to LE:5 (case study or expert opinion).


7. For each subsection, the conclusion(s) drawn from the relevant articles and evidence levels have been judged using a Grade of Recommendation (GR), ranging from a strong recommendation (Grade A) to recommendation not to do (Grade D).

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Type of evidence</th>
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<tbody>
<tr>
<td>1</td>
<td>Evidence obtained from multiple large-scale randomized controlled trials (RCT)</td>
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<tr>
<td>2</td>
<td>Evidence obtained from a single RCT or low quality RCT</td>
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<td>3</td>
<td>Evidence obtained from non-randomized controlled studies</td>
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<td>4</td>
<td>Evidence obtained from observational studies</td>
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<td>5</td>
<td>Evidence obtained from case studies or expert opinions</td>
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<td>Grade</td>
<td>Nature of Recommendation</td>
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<tr>
<td>A</td>
<td>Highly recommended to do</td>
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<tr>
<td>B</td>
<td>Recommended to do</td>
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<tr>
<td>C</td>
<td>No firm evidence for recommendation</td>
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<tr>
<td>C1</td>
<td>Can be considered</td>
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<tr>
<td>C2</td>
<td>Not recommended</td>
</tr>
<tr>
<td>D</td>
<td>Recommended not to do</td>
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</tbody>
</table>

As presented above, Level of Evidence for each reference will be made according to the following strategy in CQ6-14 (pages 24-48), however, Level of Evidence will not be shown for each reference in either “Chapter 10. Recommendation grade for treatment: Pharmacological & Conservative Treatments”, or in “Chapter 11. Recommendation grade for treatment: Surgery”.

Committee Members of Guideline (should be correctly written)

1. UAA Representative
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   Thailand, Bangladesh, Philippines

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1. Algorithms
Algorithms are made for general practitioner (GP; a) and Urologist (b-d), separately.

1.1 Treatment Algorithm of Male LUTS for General Practitioner (GP)

<table>
<thead>
<tr>
<th>Treatment Algorithm of Male LUTS/BPH (GP)</th>
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<tbody>
<tr>
<td><strong>Men &gt;40 years, s/o BPH with LUTS</strong></td>
</tr>
<tr>
<td><em>Basic Assessment: Medical History</em>, IPSS &amp; QOL, Urinalysis, Physical exam (DRE)</td>
</tr>
<tr>
<td><em>Optional Assessment: PSA</em>*, s-Cr, Post-void residual by US***</td>
</tr>
</tbody>
</table>

**Probable other disorder(s) than uncomplicated BPH (High PSA, Abnormal DRE, Hematuria, High PVR, Renal failure, Neurogenic bladder, Urothelial cancer)**

- **BPH most probable, LUTS, DRE (r/o Pca)**
  - **No**
  - **Moderate to Severe Bother (QOL>=3); Desire or Need for Treatment**
  - **Watchful Waiting**
  - **Medical Treatment with α1blocker**
  - **Specialized Management: Patient should be sent to Urologist**
  - **Continue Tx if successful**
  - **Failure (by patient’s perception)**

*Neurological disorders, Pelvic surgery, Radiation Therapy, DM, Drugs
**In patients with life expectancy of less than 10 years, or without indication for prostatic cancer treatment, serum PSA may not be routinely measured.
(See page 22, in Chapter 2. CQ5)
***Assessment of shape and size of prostate is recommended.
(See page 15 in Chapter 2. CQ2)
GP: General practitioner
DRE: digital rectal examination
1.2 Treatment Algorithm of Male LUTS; Basic Options for Urologist Using Medical/Conservative Treatments

Basic Treatment Algorithm of Male LUTS/BPH (Urologist)

*In patients with life expectancy of less than 10 years, or without indication for prostatic cancer treatment, serum PSA may not be routinely measured. (See page 22 in Chapter 2. CQ5, and page 93 in Chapter 9. Diagnosis & Investigation for BPH/Male LUTS)*

**Assessment of shape and size of prostate is recommended.***

***IPP=1 and good flow is good indication.

IPP=3 and poor flow is a potential risk for urinary retention.

IPP: Intravesical prostatic protrusion.

(See page 15 in Chapter 2. CQ2, and page 74–75 in Chapter 7. Pathophysiology of BPH)
1.3 Specialized Management for Persistent Bothersome LUTS after Basic Management for Urologist

**Specialized Management Algorithm for Persistent Bothersome LUTS after Basic Tx**

*BOO: Bladder outlet obstruction*
*PFS: Pressure-flow study*

*Urethrocystoscopy is indicated if urethral stricture or bladder neck sclerosis is suspected.*
1.4 Treatment Algorithm of Bothersome Male LUTS Refractory to Medical/Conservative Treatment or Absolute Surgical Indications for Urologist

Treatment Algorithm of Bothersome Male LUTS Refractory to Medical/Conservative Treatment or Absolute Surgical Indications

Male LUTS With indications for MIST/Surgery

- Low Surgical Risk
  - Yes
    - Surgical Risk
      - Can have surgery/general anesthesia?
        - Yes
          - Prostate Volume
            - <30ml
              - TURP
            - >80ml
              - TUBP
          - >30-80ml
        - No
          - TUEB(TUERP)
          - TUVP
          - PVP
          - Thulium laser
          - HoLEP
          - TUMT
          - TUNA
          - CIC

- High
  - Can stop anti-coagulation?
    - Yes
      - Prostate Volume
        - <30ml
          - TURP
        - >80ml
          - TUEB(TUERP)
          - TUVP
          - PVP
          - Thulium laser
          - HoLEP
          - TUMT
          - TUNA
          - CIC
    - No
      - TUEB(TUERP)
      - TUVP
      - PVP
      - Thulium laser
      - HoLEP
      - TUMT
      - TUNA
      - CIC

(Modified from EAU Guideline 2012 updated February, 2012)

- TURP: Transurethral resection of the prostate
- TUIP: Transurethral incision of the prostate
- TUEB: Transurethral enucleation of the prostate using bipolar electrode
- TUERP: Transurethral enucleation and resection of the prostate
  (either using bipolar or monopolar electrode)
- TUVP: Transurethral vaporization of the prostate
- PVP: Photoselective vaporization of the prostate
- HoLAP: Holmium laser ablation of the prostate
- HoLEP: Holmium laser enucleation of the prostate
- TUMT: Transurethral microwave thermotherapy of the prostate
- TUNA: Transurethral needle ablation of the prostate
- CIC: Clean intermittent catheterization
2. Clinical Question (CQ)
Masayuki Takeda, M.D., Ph.D., Hideki Kobayashi, M.D., Ph.D., Norifumi Sawada, M.D., Ph.D., Masaki Yoshida, M.D., Ph.D., Koji Yoshimura, M.D., Ph.D., Momokazu Gotoh, M.D., Ph.D., Japan.

As described in page 5, the recommendations of the treatments (CQ6-14) are based on a non-structured literature search, which has been previously shown, and labeled with a Level of Evidence (LE), according to a classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence, ranging from LE:1 (highest evidence level) to LE:5 (case study or expert opinion). However, Grade of Recommendations for examinations and methods for diagnosis (CQ1-CQ5) are made by the consensus of the committee members, not solely according to the above strategy.

CQ1
What questionnaires should be recommended for initial evaluation of BPH/Male LUTS ?
Answer:
IPSS: Recommendation Grade A
QOL in IPSS: Recommendation Grade A
Frequency volume chart (FVC) or Bladder diary: Recommendation Grade B
The OABSS: Recommendation Grade B

Systematic diagnostic work-up should be begun by history, validated symptom questionnaires. International Prostate Symptom Score (IPSS) and QOL score are the most prevalent, highly validated questionnaire for BPH patients [1-4]. Frequency volume chart (time and volume of voids and including any episodes of incontinence) or a bladder diary (a 24 hour recording of your liquid intake and urine output) is recommended for men with daytime or nocturnal frequency. Nocturnal polyuria (> 33% of the 24-hour urine excretion overnight) can be made only by a bladder diary, whereas the diagnosis of all other forms of non-neurogenic benign forms of LUTS in men aged 40 years or older is mainly made by exclusion. The diary records individual voiding prospectively, enabling the accurate evaluation of voiding time, individual volumes voided, and total urinary volume. This information is useful for the differential diagnosis of urinary
frequency, which can be classified as a decrease in the volume voided, polyuria, or both [5–7]. Ideally, the diary should be kept over a period of 3–7 days, although keeping the diary for over 1 or 2 days may be sufficient [8–11]. The OABSS, the sum score of four symptoms (daytime frequency, nighttime frequency, urgency, and urgency incontinence), has been developed and validated [12, 13]. OABSS can be applied efficiently to the evaluation of OAB in patients with BPH [14].

The different QOL instruments are discussed in relation to their correlation with symptom evaluation in studies of treatment options for BPH, however, there is neither agreement nor data to decide which QOL instrument is preferable. The most widely used QOL instrument is the disease-specific QOL, single question added to the IPSS, and BPH Impact Index (BII). Symptom-specific QOL is also used. Disease-specific QOL domains (interference with daily activities) tend to improve more with treatment interventions than general health measures (i.e. general well-being). Symptom-specific QOL of BPH patients cannot be estimated by physically measurable variables [15–17].

References of CQ1


CQ2
Should ultrasonography be recommended for the anatomical evaluation of BPH?

Answer:
Ultrasonography (IPP, Prostate volume) is recommended for the anatomical evaluation of the prostate (Recommendation Grade A).

Compared with a digital rectal examination and other imaging tests, ultrasonography is more accurate and minimally invasive [1–3]. Transabdominal ultrasonography is easily performed and readily able to detect both bladder pathology, and kidney lesion, whereas trans-rectal ultrasonography permits the detailed imaging of the inner structures. The type of ultrasonography performed depends on the equipment available, as well as on the objective of the examination. PV is predictive of both clinical progression and the therapeutic outcomes of surgical or medical treatment [4, 5].

Urethrography provides information in the post prostatectomy patients with residual symptoms [6, 7].
Intravesical Protrusion of Prostate (IPP) is the distance measured from the tip of the protruding lobes to the base of the prostate at the circumference of the bladder, seen in the sagittal view on transabdominal ultrasonography. A grading system for IPP is well established. Grade 1 IPP is 5mm or less, grade 2 IPP is more than 5mm to 10mm, grade 3 IPP is more than 10mm. Recent studies have shown good correlation between IPP grade and urodynamic evidence of obstruction [8–10].

For the estimation of histologically measured components, various ultrasoundographic parameters obtained by transrectal method (TRUS) were effectively compared with using ultrasonic power Doppler imaging (PDI) of the prostate [7]. CT scans and MR imaging are expensive and have no routine use in evaluating patients with BPH [6].
Ultrasound derived measurements of bladder and detrusor wall thickness, and ultrasound estimated bladder weight is potential noninvasive clinical tools for assessing the lower urinary tract [11, 12].
Retrograde urethrography has no routine use except for the case highly suspicious of urethral stricture.
References of CQ2

CQ3
Should evaluation of upper urinary tract be recommended in the initial evaluation of all BPH/Male LUTS patients?

Answer:
Routine evaluation of the upper urinary tract is not recommended in the initial evaluation.
It is recommended for men with abnormal urinalysis, a large amount of PVR, renal insufficiency, symptoms suggestive of upper urinary tract disorder (stone, cancer, infection and so on) or a history of other urological diseases (Recommendation Grade B).

A structured MEDLINE review of the literature on the association between BPH and CRF from 1966 to 2003 was performed. The extent of the association between BPH and CRF is unknown and more community based, observational studies are needed. However, an association exists and it should be considered in men presenting with obstructive BPH or CRF [1].
Discharges for primary BPH with acute renal failure increased >400% (OR 4.28, 95% CI 3.22-5.71, P-trend <0.001) from 1998 to 2008 in USA. Severe AEs of BPH persist despite widespread use of oral therapies in the USA [2].
Renal ultrasonography in 556 men with BPH detected hydronephrosis, renal cysts, and renal cancer in 2.5, 11.7 and 0.18% of men, respectively [3].
According to those data, evaluation of the upper urinary tract is not to be performed routinely. It is recommended for men with abnormal urinalysis, a large amount of PVR, renal insufficiency, or a history of other urological diseases. In these cases, ultrasonography is recommended as the initial method of assessment [4, 5].

References of CQ3
3. Koch WF, Ezz el Din K, De Wildt MJAM, Debruyne FMJ, De la Rosette


CQ4
In which case should urodynamic study (except for uroflowmetry) be recommended?

Answer:
Urodynamic examinations, including PFS and CMG, are recommended to delineate BOO, DU, and DO. PFS and CMG should be performed in whom DU or DO is suspected due to failure to respond to medication/surgery, or neurogenic lower urinary tract dysfunction is suspected (Recommendation Grade B).

In this section, pressure flow study (PFS) and filling cystometry (CMG) are included in the terminology of urodynamic study (UDS). TURP is effective, especially for patients with BOO. From symptoms alone, it is not possible to diagnose BOO. PFS and symptom profiles measure different aspects of the clinical condition that should be viewed separately in the evaluation and treatment decision of the patient presenting with lower urinary tract symptoms [1]. BOO and detrusor underactivity (DU) can be correctly evaluated, and outcome of surgery may be predicted by PFS. Detrusor overactivity (DO) can be evaluated by CMG. However, routine CMG or routine PFS is not necessary for initial diagnosis of BPH [2]. BOO, DU, and DO are all important prognostic variables for the surgical outcomes of BPH [3].

The surgical indication should be circumspect for patients who do not have BOO but have DO [2]. Symptom improvement is less likely for men with no or equivocal BOO compared with men with evident BOO [4].

Both DU without BOO and DO without BOO strongly predict treatment failure for TURP [5]. The presence of a higher degree of BOO is associated with improvements in both symptoms and QOL [6].

A significant proportion (23%) of the patient with symptomatic BPH was urodynamically unobstructed group to which prostatectomy should not be offered. To identify unobstructed patients, PFS is recommended in all BPH patients with dominant irritative symptoms [7].

PFS can be used to allocate patients with LUTS due to suspected BOO into different treatment arms with good clinical outcome and less complications [8].

While uroflowmetry cannot replace PFS in the diagnosis of BOO, it can provide a valuable improvement over symptoms alone in the diagnosis of the cause of
lower urinary tract dysfunction in men presenting with LUTS. Predicting BOO using simpler parameters such as uroflowmetry and PV may be a viable alternative because of the invasiveness of PFS and CMG [9]. The ICS-‘BPH’ Study provided performance statistics for Qmax with respect to BOO: such statistics may be used to define more accurately the presence or absence of BOO in men presenting with LUTS [10].

References of CQ4

Should serum PSA be measured in BPH/Male LUTS patients?

Answer:
In the patients at risk of prostate cancer, measurement of serum PSA concentration is strongly recommended (Recommendation Grade A). However, factors affecting on serum PSA concentration, such as enlarged prostate volume, urinary retention, prostatitis/UTI, and treatment with 5ARIs should be considered.
In patients with life expectancy of less than 10 years, or without indication for prostatic cancer treatment, serum PSA may not be routinely measured.

As higher serum PSA concentrations are indicative of prostate cancer [1–3]), and useful for estimation of enlarged prostate volume [4]. Not only prostate cancer, serum PSA concentrations are increased in men with enlarged adenoma, urinary retention, prostatitis, and massage of prostate [5]. On the other hand, anti-androgens or 5ARIs can reduce the PSA concentrations by approximately 50% [6–10]. In patients treated with the drugs, careful follow-up of serum PSA concentrations should be needed.

References of CQ5
5. Gretzer MB, Partin AW. Prostate cancer tumor markers. In: Wein AJ,


CQ6

Is long-term treatment with $\alpha_1$ blocker recommended?

**Answer:**

Many studies have been reported regarding the efficacy and safety of $\alpha_1$ blockers up to 1 year. However, there is a relative paucity of long-term data over 3 years regarding the maintained efficacy of these drugs (Recommendation Grade A).

Most long-term studies for the efficacy of $\alpha_1$ blockers are open-label extension studies of the previous short-term trials [1, 2] or retrospective studies in clinical practice. The studies showed that the efficacy and safety of $\alpha_1$ blockers up to 1 year. In long-term studies (over 3 years; range 4–10 years), the withdraw rates were approximately 18, 64, and 36–80% of patients in 2, 3, and >4 years after starting of the studies, respectively [3–6]. The risk factors for treatment failure were severe LUTS, low urinary flow rate, large prostate volume (>30–40 mL), large PVR or a history of urinary retention, concomitant OAB symptoms, urodynamically proven BOO, and insufficient effects with short-term therapy [5–7]. In the comparative long-term studies of mono- and combination treatment with $\alpha_1$ blockers and 5ARI, the efficacy of $\alpha_1$ blockers appears to be maintained over at least 4 years [8, 9]. However, the combination therapy was significantly effective as compared with $\alpha_1$ blocker mono-therapy. It may suggest that the long-term efficacy of $\alpha_1$ blockers mono-therapy is not sufficient. Alpha-1 blockers do not prevent acute urinary retention in long-term studies, so that eventually some patients will have to be surgically treated [8].

**References of CQ6**


CQ7
Is long-term treatment with 5ARI recommended?

Answer:
5ARIs should be offered to men who have moderate-to-severe lower urinary tract symptoms and enlarged prostates (≥ 30 mL) or elevated serum PSA concentrations (> 1.4 – 1.6 µg/L). Efficacy for subjective and objective parameters of long-term treatment is reported. Long term treatment of 5ARIs can also prevent disease progression with regard to acute urinary retention and the need for surgery (Recommendation Grade B).

After 2 to 4 years of treatment, 5ARIs reduce LUTS (IPSS) by approximately 15-30%, decrease prostate volume by approximately 18-28% and increase Qmax of free uroflowmetry by approximately 1.5-2.0 mL/s in patients with LUTS due to prostate enlargement [1–10].
Comparative studies with α1 blockers have demonstrated that 5ARIs reduce symptoms more slowly and, for finasteride, less effectively [1, 2, 7]. A long-term trial with dutasteride in symptomatic men with a prostate volume ≥ 30 mL (average prostate volume in the CombAT trial was approximately 55 mL) showed that the 5ARI reduced LUTS in these patients at least as much or even more effectively than tamsulosin [8, 9]. The greater the baseline prostate volume (serum PSA concentration), the faster and more pronounced the symptomatic benefit of dutasteride [11]. 5ARIs, but not α1 blockers, reduce the long-term (> 1 year) risk of acute urinary retention or need for surgery [5, 7, 11, 12]. Prevention of disease progression by 5ARIs is already detectable with prostate sizes considerably smaller than 40 mL [9, 10, 12]. The precise mechanism of action of 5ARIs in reducing disease progression is unclear, but it was demonstrated that reductions of voiding parameters after computer-urodynamic re-evaluation in men who were treated at least 3 years with finasteride [13, 14, 15].

References of CQ7


**CQ8**

Is anticholinergic monotherapy recommended for BPH/OAB patient?

**Answer:**

Monotherapy of anticholinergic drugs might be considered in men with moderate to severe lower urinary tract symptoms who have predominantly bladder storage symptoms. However, careful follow-up is recommended in men with bladder outlet obstruction. Low grade IPP with good flow rate is indication for anti-cholinergic monotherapy (Recommendation Grade B)

The efficacy of the anticholinergic drugs was tested as a single agent in adult men with bladder storage symptoms (OAB symptoms) but without bladder outlet obstruction. In open-label trials with tolterodine, daytime frequency, nocturia, urgency incontinence, and IPSS were all significantly reduced compared to baseline values after 12-25 weeks [1, 2]. In an open-label study with α1 blocker non-responders, each storage and voiding symptom of IPSS was improved during tolterodine treatment [1]. Randomized, placebo-controlled trials demonstrated that tolterodine can significantly reduce urgency incontinence and daytime or 24-hour frequency compared to placebo. It was also demonstrated that urgency related voiding is significantly reduced by tolterodine [3–5]. Treatment outcome analyzed by PSA-concentration (prostate volume), tolterodine significantly reduced daytime frequency, 24h voiding frequency and IPSS storage symptoms only in those men with PSA concentrations below 1.3 ng/mL indicating that men with smaller prostates might profit more from anticholinergic drugs [6]. Increase of post-void residual urine in men without bladder outlet obstruction is minimal and not significantly different compared to placebo (0 to 5 mL vs. -3.6 to 0 mL). However, fesoterodine 8 mg showed higher post-void residuals (+20.2 mL) compared to placebo (-0.6 mL) or fesoterodine 4 mg (+9.6 mL) [7]. The incidence of urinary retention in men treated with tolterodine without bladder outlet obstruction was comparable with placebo (0 to 1.3 vs. 0 to 1.4%). In men under fesoterodine 8 mg treatment, 5.3% had symptoms suggestive of urinary retention that was higher compared to placebo or fesoterodine 4 mg (0.8% each). In men with bladder outlet obstruction, anticholinergic drugs are not recommended due to the theoretical decrease of bladder strength which might be associated with post-void residual urine [8] or urinary retention. In addition, long-term studies on the efficacy of muscarinic
receptor antagonists in men with LUTS/BPH are still missing, therefore, these drugs should be prescribed with caution, and regular re-evaluation of IPSS and post-void residual urine is advised. For patients complaining nocturia, not OAB, desmopressin is effective for nocturia due to nocturnal polyuria [9–12].

References of CQ8


CQ9
In which case should combination use of α1 blocker and 5ARI be recommended?

Answer:
Combination use of α1 blocker and 5 alpha-reductase inhibitors (5ARIs) are recommended for symptomatic BPH, especially for patients with a relatively large-sized prostate. (Recommendation Grade A)
Non-selective α1 blockers have a potentially higher risk of orthostatic hypotension.

The Medical Therapy of Prostatic Symptoms (MTOPS) study was a double-blind trial involving 3047 men to compare the effects of placebo, doxazosin, finasteride and combination therapy on measures of the clinical progression of BPH [1]. Inclusion criteria were age ≥50, IPSS ≥8 and a maximum urinary flow rate between 4 and 15 mL/s, and the mean follow-up was 4.5 years. The reduction in risk of clinical progression associated with combination therapy (66%) was significantly greater than that associated with doxazosin (39%, p<0.001) or finasteride (34%, p<0.001) alone. The improvement in symptoms scores of combination therapy (-7.4 at 4 years) was significantly greater than doxazosin (-6.6, p=0.006) and finasteride (-5.6, p<0.001) alone. The rates of adverse events were higher in combination therapy group than in each single treatment groups, in the aspects of abnormal ejaculation, peripheral edema and dyspnea.

The Combination of Avodart® and Tamsulosin (CombAT) study was a 4-yr., multicenter, randomized, double-blind, parallel-group study in 4844 men ≥50 years of age with a clinical diagnosis of BPH, IPSS ≥12, prostate volume ≥30mL, PSA 1.5-10 ng/mL and maximum urinary flow rate >5 and ≤15 mL/s with minimum voided volume ≥125mL [2]. At 4 yr., combination therapy was significantly superior to both monotherapies at reducing the relative risk of BPH progression (31% from dutasteride, 44% from tamsulosin), and provided significantly greater symptom benefit (-6.3) than dutasteride (-5.3, p<0.001) and tamsulosin (-3.8, p<0.001) alone. The occurrence of drug-related adverse events was significantly greater in the combination group. However, withdrawal rates due to drug-related adverse events were similar across treatment groups (4-6%). These observations were also similar in Asian men [3].
In both trials, post hoc analyses showed that patients with larger prostate volume (≥25 mL in MTOPS study, and ≥40 mL in CombAT study) at baseline had a greater benefit in reduction of clinical progression from combination therapy than those with small prostate [4, 5]. Analyses on cost-effectiveness of combination therapy using Norwegian model estimated that incremental cost-effectiveness ratios, which means the cost per quality-adjusted life-years (QALYs) gained, are higher in combination therapy than in alpha blocker monotherapy both at 4 years and at the lifetime. However, the incremental QALYs gained for combination therapy are twice those of α1 blocker monotherapy. If willingness to pay per QALY gained is above €6000, fixed-dose combination therapy with dutasteride becomes the preferred treatment [6].

References of CQ9
5. Roehrborn CG, Barkin J, Siami P et al. Clinical outcomes after combined therapy with dutasteride plus tamsulosin or either monotherapy in men with benign prostatic hyperplasia (BPH) by baseline characteristics: 4-year results from the randomized, double-blind Combination of Avodart and Tamsulosin (CombAT) trial. BJU Int. 2011; 107: 946–54. (1)
findings of the Combination of Avodart and Tamsulosin trial. BJU Int. 2012; 109: 731–8.
In which case should combination use of $\alpha_1$ blocker and anticholinergic drug be recommended?

**Answer:**

Patients with LUTS/BPH associated with OAB are recommended to use combination of $\alpha_1$ blocker and anticholinergic drug. There are sufficient evidences supporting the efficacy and safety of combination therapy with $\alpha_1$ blocker and anticholinergic drug for LUTS/BPH associated with OAB. Especially, the patients still having OAB symptoms after $\alpha_1$ blockers treatment are good candidates for the combination treatment. (Recommendation Grade B). Low grade IPP with good flow is an indication for combination therapy.

It is suggested that 50-70 % of patients with BPH have OAB symptoms [1]. For male OAB symptoms, monotherapy with $\alpha_1$ blockers is effective and may be a first line treatment [2], although the efficacy of $\alpha_1$ blockers is limited for patients with detrusor overactivity [3]. Several reports suggested that combined therapies with anticholinergic drugs and $\alpha_1$ blockers are more effective than monotherapy with $\alpha_1$ blockers in improving storage symptoms, with urinary retention being rare [4–13]. Meta-analysis of the combination therapy showed that the therapy did not affect to urinary flow rate, increased average post-void residual urine by 11.6mL, and caused urinary retention just 0.3% [14]. Urodynamic study showed that combination therapy increased bladder volume at the first involuntary contraction and maximum bladder capacity [7]. Although the combination therapy did not cause the change of total IPSS, it improved the storage sub-score [8]. There remains a concern about the exacerbation of voiding difficulties and possible urinary retention in a practice setting [2]. Grade 3 IPP is risk factor for possible urinary retention with combination therapy.

**References of CQ10**

3. Lee JY, Kim HW, Lee SJ, Koh JS, Suh HJ, Chancellor MB. Comparison of
doxazosin with or without tolterodine in men with symptomatic bladder outlet obstruction and an overactive bladder. BJU Int. 2004; 94: 817–20. (2)


12. Nishizawa O, Yamaguchi O, Takeda M, Yokoyama O, for the TAABO Study Group. Randomized controlled trial to treat benign prostatic hyperplasia with
overactive bladder using an alpha-blocker combined with anticholinergics. LUTS 2011; 3: 29–35. (2)


CQ11
In which case should surgical intervention be recommended?

This CQ should be modified into 2 categories;
In which case should surgical intervention be recommended?
1. Absolute indications?
2. Relative indications?

Answer:
Absolute indications are patients with refractory urinary retention, recurrent UTI, vesical stone, renal insufficiency, refractory gross hematuria (Recommendation Grade A).
Relative indications are patients unresponsive to medical treatment, or patients who cannot maintain medical treatments due to adverse events, or patients who are not satisfied with medical treatments.
Pressure-flow study is recommended in order to rule out detrusor underactivity and overactivity. IPP should be correctly evaluated when surgery is planned.

Recurrent spontaneous urinary retention after failure of trials without catheter is an indication of surgical intervention (see CQ13). Similarly, surgery would be better to be considered in patients with hydronephrosis and/or renal function impairment due to chronic bladder outlet obstruction (BOO) from BPH, gross hematuria, bladder stone and recurrent urinary tract infection, whereas these indications are empirical and not supported by clinical evidences [1].
Patients resistant to medical treatment are relative symptom-based indication of surgery. However, male lower urinary tract symptoms are not always associated with BOO or BPH [2]. Approximately 15% of patients undergoing surgery do not profit in improvement of symptoms [3, 4]. Pressure-flow study (PFS) is an important examination to provide objective information [4–6], and BOO, detrusor underactivity (DU) and detrusor overactivity (DO) are key conditions to predict outcome of surgery. However, it is still under debate whether this examination is essential for judge of surgery [7, 8]. Although BOO is not an essential condition for TURP, the degree of symptom improvement in patients without BOO is approximately 70% of that in patients with BOO [6, 9]. DU, DO and absence of BOO are independent risk factors for poor outcome of surgery [10].
Nocturia is the symptom least sensitive to treatment for BPH [11, 12]. When nocturia remains as a main symptom after medical treatment for BPH, conditions other than BPH, such as lowering functional bladder capacity, polyuria, nocturnal polyuria and sleep disturbance, should be ruled out before decision of surgical intervention. Frequency volume charts are recommended to use to detect such conditions.

References of CQ11
**CQ12**

Which interventions are recommended for urinary retention in BPH patients?

**Answer:**

Initially, immediate bladder decompression by catheterization should be performed. Treatment with α1 blockers before a trial without catheter (TWOC) is recommended after that. Surgical intervention for BPH is required for patients with a TWOC failure. Duration of catheterization should be shortened to reduce the comorbidity. (Recommendation Grade B)

Acute urinary retention (AUR) due to BPH should be initially managed by immediate bladder decompression. Urethral catheterization is exclusively more chosen by urologists or emergency room physicians than suprapubic catheterization world widely [1], and suprapubic catheterization is associated with significantly high rate of hematuria, impossible catheterization and catheter obstruction [2].

A trial without catheter (TWOC) is the next step. Treatment with α1 blockers for 2-3 days before catheter removal should be strongly recommended, since it significantly increases success rate of TWOC [1, 3, 4]. Duration of catheterization should be shortened, since catheterization for 4 days or longer is associated with significantly higher rate of asymptomatic bacteriuria, lower urinary tract infection, urine leak, catheter obstruction and prolongation of hospitalization for adverse events [1]. After failure of first TWOC, second and third TWOC can succeed. However, the rate of success of second and third TWOC is not high and most patients with TWOC failure require surgical intervention [1]. Even after success of TWOC, half patients require surgical intervention during long-term follow-up [5].

Risk factors for failure of TWOC are older age (≥70y, OR 1.4), spontaneous AUR (OR 1.4), large amount of drained volume (≥1000mL, OR 1.6), severe LUTS before AUR (OR 1.6) and large prostate volume (>50mL, OR 1.6) [1].

**References of CQ12**


Which therapies are recommended for BPH patients who are not fit for surgery due to severe comorbidities?

**Answer:**

For surgery-unfit patients, alternative therapies are recommended according to individual medical and social conditions of patients. Each option, such as urethral stent placement, intermittent catheterization, urethral catheter placement, suprapubic cystostomy placement, and other minimal invasive surgical therapies (TUMT, TUNA), have their respective benefits and drawbacks. (Recommendation Grade C1)

There are patients with severe LUTS or complications of BPH in whom medical therapy fails and for whom surgery is deemed a high risk. Alternative options for such unfit patients include urethral stent placement, intermittent catheterization, intra-prostatic ethanol injection, intra-prostatic botulinum toxin injection, urethral catheter placement and suprapubic cystostomy placement. Various types of urethral stent are available, and they can be used temporarily (such as Prostakath™, ProstaCoil™ and Memokath™) or permanently (such as Memokath™, UroLume™ and Memotherm™). Placement of stents is generally safe and significantly improves obstructive symptoms [1]. However, the rate of complications including removal due to stent malposition/migration, gross hematuria, vesical irritability, symptomatic urinary tract infection, and stone formation is not low during follow-up [2–5].

Clean intermittent catheterization is another option for surgery-unfit BPH. There are few evidences of superiority of intermittent catheterization to continuous catheterization for BPH patients. However, there are several RCTs showing superiority of intermittent catheterization with regard to bacteriuria and urinary tract infection in other diseases [6, 7]. Therefore, if possible, this technique should be considered. Dementia, motor paralysis of upper limbs and visual impairment do not allow patients to perform self-catheterization. When medical and/or social condition cannot afford intermittent catheterization, continuous indwelling of urethral catheter could be considered, while this method is liable to various complications, including acquired hypospadias, cutaneourethral fistula, and vesical stone formation [8]. Suprapubic cystostomy has a further higher rate of stone formation than urethral catheterization [9].
Intraprostatic ethanol injection [10] and botulinum toxin injection [11] are promising alternatives for surgery-unfit patients, while they are considered still experimental. Transurethral microwave thermotherapy (TUMT) and transurethral needle ablation (TUNA) are indicated in high risk patients especially having bleeding tendency and volume overload [12]. These kinds of treatment can be performed without anesthesia. Due to less improvement of symptoms [13], when compared to standard treatment and introduction of any kind of laser therapy, TUMP is performed less frequent during the last decade. TUNA is considered contraindicated in prior radiation to pelvic organ due to higher risk of rectal fistula [14].

References of CQ13
What therapeutic strategies are recommended to avoid sexual dysfunction as an adverse event?

**Answer:**

Watchful waiting (active surveillance) could be considered for avoidance of any sexual dysfunction. Alpha 1 blockers could be recommended for patients who care erectile dysfunction. Tamsulosin and silodosin are liable to ejaculation dysfunction. 5 alpha-reductase inhibitors could cause erectile dysfunction and decrease of libido.

Phosphodiesterase type 5 inhibitor, Tadalafil, has been approved for BPH/Male LUTS in USA and some Asian countries in 2011. Tadalafil is effective in both LUTS and ED, but has not been approved in most Asian countries.

Surgical therapy can induce ED, and it generally result in ejaculation dysfunction. Although the incidence of sexual adverse events by minimally invasive treatments, such as transurethral microwave therapy (TUMT) and transurethral needle ablation (TUNA), is lower, these types of treatment cannot always avoid adverse events on sexual function.

(Recommendation Grade B)

If a patient has only mild lower urinary tract symptoms owing to BPH and cares sexual dysfunction due to interventional therapy, watchful waiting is a potential option.

Alpha 1 blockers, such as alfuzosin and doxazosin, have generally beneficial effects on erectile function [1–4]. Further, the incidence of erectile dysfunction (ED) induced by \(\alpha 1\) blockers is not so high (0.6-12%) and similar to that by placebo [4]. Therefore, \(\alpha 1\) blockers can be recommended to use for patients who care ED. Although non-selective A1Bs, such as alfuzosin and doxazosin, have no increased risk of ejaculation dysfunction (EjD) (0-1.3%) [5], \(\alpha 1\) blockers selective for alpha-1A adrenoreceptor, including tamsulosin (~30%) [5] and silodosin (~28%) [6] are associated with increased risk of EjD. 5 alpha-reductase inhibitors (5ARIs), finasteride and dutasteride, can induce several types of sexual dysfunction, i.e. ED, EjD, and decrease of libido [7, 8]. The incidence of drug-related sexual adverse events decreases with longer duration of therapy [9, 10]. Phosphodiesterase type 5 inhibitors, such as sildenafil, vardenafil and
tadalafil, have promising effects both on lower urinary tract symptoms due to BPH and erectile function [11, 12]. However, this type of drugs is approved for treatment for LUTS in no Asian countries. The incidence of ED by open prostatectomy and transurethral resection of the prostate (TURP) is reported 3 to 20% [13, 14]. However, similar percentages of patients could experience the improvement of erectile function by TURP [14]. These standard surgical treatments inevitably result in EjD (~80%) [14]. Surgeries using holmium: YAG-laser (ablation; HoLAP, resection: HoLRP, enucleation: HoLEP) or KTP-laser (vaporization; PVP) have similar effect on sexual function to TURP [13]. On the other hand, several minimally invasive methods, such as transurethral microwave therapy (TUMT) and transurethral needle ablation (TUNA), have lower incidence of adverse events on sexual function [14].

References of CQ14

5. AUA Clinical Guidance, Management of BPH (Revised 2010), Final Appendices (http://www.auanet.org/content/clinical-practice-guidelines/clinical-guidelines.cfm?sub=bph) (Guideline)


3. Introduction
Masayuki Takeda, M.D., Ph.D., Hideki Kobayashi, M.D., Ph.D.,
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An increase in the prevalence of lower urinary tract symptoms (LUTS) with age in men [1] is seen, and which is important given the increase in the aging population [2]. Because of the great prevalence of benign prostatic hyperplasia (BPH) in elderly men, which is as high as 40% in men in their fifth decade and 90% in men in their ninth decade [3], the most important and prevalent cause of LUTS in men over 40 years is generally believed to be the enlarging prostate/BPH. Although BPH is a histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone [4, 5], benign prostatic enlargement (BPE), or benign prostatic obstruction (BPO) are often used in the same way as BPH in the clinical setting. Recently, the causes of aging male LUTS are known to be multifactorial, and LUTS may be linked to the prostate (BPH-LUTS), bladder (detrusor overactivity-overactive bladder syndrome [OAB], detrusor underactivity), kidney/heart (nocturnal polyuria), or brain (sleep disorder) [6]. Usually, more than one of those factors is present, in a patient complaining of LUTS. According to such situation, the title of the 1st UAA Guideline has been determined as “BPH/Male LUTS”, not solely “BPH”, and the Purposes of this guideline is to summarize Practical Consensus Statement on the Management of BPH/Male LUTS from UAA. Target doctors are both Urologists and non-Urologists/General Practitioners, and target patients are 40 years or older male patients with BPH/LUTS. Traditionally in Asian countries, socio-cultural atmosphere of accepting lower urinary tract symptoms (LUTS) as a natural part of aging process has been dominant. However, far Eastern countries like Japan, Korea and Taiwan have already become an “aging society” and the ever-growing public interest in their health and well-being, public awareness towards BPH has been increasing rapidly along with the number of patients who visit hospitals seeking medical care for LUTS. Thus, it can be expected that BPH will soon become a major issue with regard to public health and welfare in all Asian countries, as is already the situation for many Western countries. The UAA Guideline on Male LUTS mainly covers LUTS secondary to benign prostatic enlargement (BPE) or benign prostatic obstruction (BPO), detrusor overactivity or overactive bladder (OAB), and nocturia due to nocturnal polyuria. Other causes of male LUTS are covered by separate EAU Guidelines.
3.1 Multifactorial Etiology of LUTS

Multifactorial Etiology of Lower Urinary Tract Symptoms

- All Men >40 yrs
- BPE: benign prostatic enlargement
- BOO: bladder outlet obstruction
- Histological BPH
- LUTS: lower urinary tract symptoms
- OAB: overactive bladder

(Modified from Abrams P et al. Male lower urinary tract dysfunction, 73, 2006)

3.2 Multifactorial conditions for LUTS

Multifactorial Conditions which can result in LUTS

- OAB/Detrusor Overactivity
- Benign Prostatic Obstruction
- Nocturnal Polyuria
- Sleep Disorder
- Neurological Diseases
- Hormonal Changes
- Ischemia
- Others?

(LUTS: lower urinary tract symptoms)
References
4. Definition, and terminology of benign prostatic hyperplasia (BPH) and related disorders
Salam, M.A., MD, Md Afiquor Rahman, MD

In the past, a number of terms such as prostatism, symptomatic benign prostatic hyperplasia (BPH), and clinical BPH have been used to describe symptoms related to micturition in older men. Currently, the traditional belief that urinary symptoms in elderly men were always assumed to be directly or indirectly related to prostate has been challenged. The term lower urinary tract symptoms (LUTS) has been adopted and several consensus and guidelines committees have attempted to define the appropriate terminology for categorizing the pathophysiological conditions underlying male LUTS [1–5].

4.1 The term lower urinary tract symptoms (LUTS; as defined by the International Continence Society) are the subjective indicator of a disease or change in condition as perceived by the patient, caregiver or partner and may lead him/her to seek help from health care professionals. LUTS can be classified as storage, voiding, and post micturition symptoms.

4.2 Bladder storage (irritative) symptoms are experienced during the storage phase of the bladder and include: increased daytime frequency, nocturia, urgency, and urinary incontinence.

4.3 Voiding (obstructive) urinary symptoms are experienced during the voiding phase and include: slow urinary stream, splitting or spraying of the urinary stream, intermittent urinary stream, hesitancy, straining to void, and terminal dribbling.

4.4 Post micturition symptoms include feeling of incomplete emptying and postmicturition dribbling.

4.5 Benign prostatic hyperplasia (BPH) represents a histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone. Benign prostatic hyperplasia or BPH is a term used (and reserved for) the typical histological pattern, which defines the disease. BPH progression is a dynamic process that includes deterioration of LUTS and
health related quality of life, increased prostatic size, acute urinary retention (AUR), and BPH-related surgery. Renal insufficiency and recurrent urinary tract infections as additional measures of BPH progression have also been considered. However, these outcomes are rarely observed [6–9].

4.6 **Benign prostatic enlargement (BPE)** is defined as prostatic enlargement due to histologic benign prostatic hyperplasia. The term “prostatic enlargement” should be used in the absence of typical prostatic histology.

4.7 **Bladder outlet obstruction (BOO)** is the generic term for obstruction during voiding and is characterized by increased detrusor pressure and reduced urine flow rate. Therefore, the term BOO requires urodynamic confirmation.

4.8 **Benign prostatic obstruction (BPO)** is bladder outlet obstruction (needs urodynamic evaluation) and may be diagnosed when the cause of outlet obstruction is known to be benign prostatic enlargement, due to histologic benign prostatic hyperplasia. The relationship between LUTS, BPH, BPE, BOO and BPO is complex and not fully understood. Because the prevalence of histological BPH and LUTS is age-related, it was often assumed that they were causally related, but recent evidence indicate that male LUTS may result from a complex interplay of pathophysiological influences, including prostatic pathology and bladder dysfunction. However, BPH is the primary cause of LUTS in older men. Most men with enlarged prostates may not have any symptoms at all. BPO may occur in some but not all men with BPH and LUTS. The elderly men with BPH may not develop BOO which is characterized by increased detrusor pressure and reduced urine flow rate. Many men develop BPO without evidence of histologically proven BPH. BOO due to BPE may have both static (increased tissue mass) and dynamic (increased smooth muscle tone) components in the prostate leading to variable lower urinary tract symptoms. BOO due to BPE or BPH may lead to overactivity of the detrusor muscle leading to irritative symptoms predominantly. This situation may not be clarified with conventional investigations of BPH. An urodynamic studies will settles the issue by confirming the overactivity of the bladder is due to benign prostatic obstruction [10, 11].
References


5 Risk Factors for BPH
Jose Albert C. Reyes III, MD, DPBU, FPUA, FPCS

Evidence suggests that modifiable factors such as obesity, diet, dyslipidemia, hormonal imbalance, hypertension, metabolic syndrome, alcohol and smoking contribute to the development of BPH and/or LUTS other than aging and androgens [1].

5.1 Genetic Factors:
Partin and colleagues demonstrated a concordance for benign prostate disease in monozygotic (MZ) and dizygotic (DZ) twins who served in the United States military in World War II [2]. Genetic factors not only determine risk for development of BPH but also affect its presentation and severity. Also, Meikle and colleagues demonstrated that heritability appears to account for 82.6% of the variability in symptom score in men older than 50 years in a study conducted on twins. Table 1 summarizes Family History of Early-Onset BPH Increases Risk of Clinical Significant BPH (Table 1) [3].

5.2 Dietary Factors:
Those with high intake of protein and polyunsaturated fatty acid appear to be at greater risk of developing BPH [4].
Marchard et al evaluated the relation between consumption of high animal fat products to BPH and prostate cancer. It was proposed that certain aspects of western diet, low amount of fruits and vegetables and a higher proportion of energy from animal fats, explain the epidemiologic evidence linking western dietary patterns to a higher BPH risk [5, 6]. Daily fruit consumption was later then found out to be inversely related to risk of BPH [7]. Furthermore, Galuzzi et al found that Southeast Asian men have a lower prevalence and severity of autopsy-diagnosed BPH than age-matched North American men [8], implying that ethnicity and geographical factors, such as migration, can influence the growth of the normal human prostate during midlife [9]. Chyou examined 33 food items in relationship to prostatectomy rates and found only beef intake significantly associated [10]. Araki and associates reported increased clinical diagnosis of BPH in men with higher milk consumption and lower consumption of green and yellow vegetables [11]. Overall there is no convincing evidence for any individual diet factor to play
a major role in the development of LUTS/BPH.

5.3 Obesity, Hypertension, DM, Hypercholesterolemia and Sexual Dysfunction:
The relationships between LUTS/BPH and obesity, BMI, and the metabolic syndrome have recently been of great interest [12–15]. Autonomic hyperactivity has been implicated in the development of both LUTS and ED in the aging male, but conclusive clinical data are lacking [16]. In the EpiLUTS study both heart diseases and hypertension were associated with more severe LUTS constellations [17]. Dyslipidemia has also been associated with an increased risk of BPH [18] (See Appendix- Table II). In a cohort in 1998 involving Swedish men with BPH lower HDL, higher LDL, and higher triglycerides were associated with increased prostate volume [19]. A pilot case-control study showed that higher triglyceride levels, high waist-to-hip ratio, and lower HDL levels were associated with BPH in North Indian population [20]. Hammarsten and Hogstedt examined 250 patients with LUTS and found non–insulin-dependent diabetes mellitus, hypertension, tallness, obesity, high insulin level, and low high-density lipoprotein cholesterol levels to be risk factors for the development of BPH and suggested a causal relationship between high insulin levels and the development of BPH and hypothesize increased sympathetic nerve activity in men with BPH [21].

5.4 Other risk factors:
Physical activity thus appears to reduce the risks of BPH and LUTS. Similar findings of increased likelihood of LUTS with increasing BMI and decreasing likelihood with greater physical activity were also reported from the EpiLUTS study [17]. Alcohol intake may lower incidence of BPH by decreasing plasma testosterone production and increasing testosterone clearance. In an analysis of the Prostate Cancer Prevention Trial, alcohol appears to have a somewhat protective effect against BPH [22]. Studies on the relationship of liver cirrhosis and BPH, revealed a lower incidence of BPH in men with cirrhosis [22–25]. However, multivariate analysis show and increase surgical risk for BPH in patients taking in more than three glasses of alcohol per day [26, 27]. Cigarette smoking appears to have a protective effect on prostatism at certain smoking intensities, but no effect or a deleterious effect at other intensities [28–30]. Light or moderate smokers are less likely to have moderate to severe
prostatism, whereas heavy smokers are at least as likely to have moderate to severe prostatism compared with never-smokers [31]. Cold medications containing α-sympathomimetic drugs exacerbate LUTS by the expected effect on the smooth muscles of the bladder outlet. Recently a careful analysis of the data from the Olmsted County study demonstrated that daily use of antidepressants, antihistamines, or bronchodilators is associated with a 2- to 3-point increase in the IPSS compared with age-matched nonusers and daily use of antidepressants is associated with a decrease in the age-adjusted flow rate [32].

It was reported that there is 49% reduction in risk for prostatectomy in widowed versus single men [33]. Cross-sectional data from the Olmsted County study suggest that the frequency of ejaculation has no effect on LUTS, peak urinary flow rates, or prostate volume; the apparent protective association appears to be an artifact caused by the confounding effects of age [34]. Impact of some socioeconomic factors on LUTS and BPH had deepened with the help of two studies, the European Prospective Investigation into Cancer and Nutrition (EPIC) and the Epidemiology of Lower Urinary Tract Symptoms (EpiLUTS), and the Boston Area Community Health (BACH) studies [35, 36]. Araki and associates found higher rates of BPH in higher income groups [10], whereas, in contrast, Glynn and coworkers reported higher rates of surgery in lower income groups which could be because higher income groups might have better access to health care whereas lower income groups might submit more readily to the suggestion of a surgical procedure [37].
## APPENDIX

### Table I. Family History of Early-Onset BPH Increases Risk of Clinical Significant BPH

<table>
<thead>
<tr>
<th>Relatives with history of prostatectomy (open or transurethral) for BPH</th>
<th>RELATIVE RISK of CLINICAL BPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>All first-degree male relatives</td>
<td>4.4</td>
</tr>
<tr>
<td>Fathers of proband</td>
<td>3.5</td>
</tr>
<tr>
<td>Brothers of proband</td>
<td>6.1</td>
</tr>
</tbody>
</table>

[3]

### Table II. Modifiable Risk Factor Associated with Decreased or Increased Risk of LUTS and/or BPH

<table>
<thead>
<tr>
<th>STUDY</th>
<th>RISK FACTOR</th>
<th>REFERENCE CATEGORY</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Professionals Follow-up</td>
<td>Clinical BPH: Alcohol intake 30.1-50 g/day Walking ≥ 2 hr/wk</td>
<td>Alcohol intake 0 g/day Walking 0 hr/wk</td>
<td>0.59 (0.51-0.70) 0.73 (0.63-0.84)</td>
</tr>
<tr>
<td>Massachusetts Male Aging Study</td>
<td>Clinical BPH (physical activity 862 kcal/day or greater)</td>
<td>Physical activity 140 kcal/day</td>
<td>0.50 (0.3-0.9)</td>
</tr>
<tr>
<td>PLCO</td>
<td>Clinical BPH (alcohol intake 60 g/day or greater) TURP likelihood (alcohol intake ≥60 g/day) Nocturia (alcohol intake ≥60 g/day)</td>
<td>Alcohol intake &lt;5 g/day Alcohol intake &lt;5 g/day</td>
<td>0.60 (0.5-0.7) 0.40 (0.3-0.7) 0.80 (0.7-1.0)</td>
</tr>
<tr>
<td>NHANES III</td>
<td>LUTS: Alcohol intake ≥1 drink/day Physical activity &gt;6 times/wk</td>
<td>Never Physical activity 0 times/wk</td>
<td>0.59 (0.36-0.97) 0.49 (0.29-0.84)</td>
</tr>
</tbody>
</table>
## References


6. Rohrmann S, Giovannucci E, Walter CW, Platz EA. Fruit and vegetable consumption, intake of micronutrients, and benign prostatic hyperplasia in


6. Epidemiology & Natural history
Shing-Hwa Lu, M.D., Ph.D., and Edward Chen, M.D., Ph.D.

The following 4 categories are discussed in this chapter.

6.1 Natural history before diagnosis
6.2 Factors affecting health-care seeking behavior
6.3 Prediction of symptomatic progression
6.4 Natural history after diagnosis

6.1 Natural history before diagnosis
Benign prostatic hyperplasia (BPH) is the most common nonmalignant condition of the prostate occurring in ageing men. Even though BPH is a major public health problem, causing high morbidity and substantial worsening in men’s quality of life [1]. The prevalence rates of BPH, depend very much on the parameters used in a case definition [2], has been estimated on the basis of results of community-based studies in Japan [3–5]. Six and 12% of Japanese men in their sixties and seventies, respectively, meet all three of the following criteria for BPH: (i) an international prostate symptom score (IPSS) >7; (ii) prostate volume (PV) >20 mL; and (iii) peak urinary flow rate (Qmax) <10 mL/s. Only 2% of men in their forties and fifties met the above criteria.

The principal risk factors for BPH are aging and normally functioning testicles. Although no definitive genes responsible for BPH have been identified, a family history of BPH and molecular abnormalities may increase the likelihood of its development. Dietary factors, such as isoflavonoids and lignans in vegetables, grains, and soy, may have a negative impact on the development of BPH [1]. Furthermore, recent studies have claimed a relationship between metabolic syndrome and BPH [6–8].

The normal prostate reaches 20 plus or minus 6 g in men between 21 and 30 years old, and this weight remains essentially constant with increasing age unless benign prostatic hyperplasia develops. The prevalence of pathological benign prostatic hyperplasia is only 8% at the fourth decade; however, 50% of the male population has pathological benign prostatic hyperplasia when they are 51 to 60 years old. The average weight of a prostate that is recognized at autopsy to contain benign prostatic hyperplasia is 33 plus or minus 16 g. Only 4% of the prostates in men more than 70 years old reach sizes greater than 100 g.
An analysis of a logistic growth curve of benign prostatic hyperplasia lesions removed at prostatectomy indicates that the growth of benign prostatic hyperplasia is initiated probably before the patient is 30 years old. The early phase of benign prostatic hyperplasia growth (men between 31 and 50 years old) is characterized by a doubling time for the tumor weight of 4.5 years. In the mid phase of benign prostatic hyperplasia growth (men between 51 and 70 years old) the doubling time is 10 years, and increases to more than 100 years in patients beyond 70 years old [9]. BPH is a physiological process that occurs with aging, regardless of race, ethnicity or region [9, 10].

Estimated prostate growth rates increased with increasing age. However, the estimated average annual change was 1.6% across all age groups. Estimated prostate growth rates were high depending on baseline prostate volume with higher growth rates for men with larger prostates [11].

BPH can be characterized as a progressive disease in a certain proportion of men older than 50 yr. Men with growing prostates are at a greater risk of symptomatic deterioration. Men who have prostates that do not grow significantly are more likely to improve symptomatically [12]. The prevalence of LUTS in the general population is age-related [4, 13, 15]. Longitudinal studies have shown an increase in IPSS with advancing age as a whole [12, 16, 17], but with simultaneous decreases in IPSS in certain subgroups [16, 18], Qmax decrease with aging [5, 19], and this may be attributable to BPO as well as detrusor underactivity (DU). Longitudinal studies have confirmed age-related increases in PV [11, 12], although in a small proportion of men PV has been noted to decrease with aging [20]. Recent studies indicate that PV is likely to increase in men in whom the prostate has a visible transition zone with a clear border [21, 22], and with a large transition zone volume on transrectal ultrasound at baseline [23]. The relationship between LUTS, urinary flow rate and PV is generally poor in men presenting at hospital, but it is modest among men in the general population. Prostate enlargement is likely to be involved in the progression of symptoms [12, 24].

6.2 Factors affecting health-care seeking behavior
A cross-sectional, population-based cohort study in Olmsted County revealed that health-care seeking behavior was influenced by the severity of symptoms, particularly if they were bothersome and interfered with an individual's daily
activities. While symptom severity is an important determinant of health care-seeking behavior for men with urinary symptoms, some additional factor or factors associated with age remain that may drive men to seek care for urinary symptoms. These factors may prove important in understanding the small-area variations in treatment of benign prostatic hyperplasia that have been noted by others. Men aged 70 to 79 years were 4.6 times as likely (95% confidence interval, 2.1 to 10.1) as men aged 40 to 49 years to have sought health care because of urinary symptoms [25]. Seventy-six% of men who had sought medical care had prostatic enlargement, depressed peak urine flow rates, or moderate-severe symptoms (sensitivity). In contrast, only 55% of men who did not seek health care for urinary symptoms had mild symptoms, normal prostatic volume, and normal peak urine flow rates (specificity). Clinical, physiologic, and anatomic measures of prostatism do not adequately distinguish the men who seek medical care for their urinary symptoms from those who do not. There remain some factor(s) that apparently lead some men with minor disease to seek care and that prevent men with measurable disease from seeking care [26].

Voiding symptoms may have impact on medical care-seeking behavior through QOL impairment in Japanese men. The QOL score appeared to reveal more pronounced differences between men in clinic and community setting than the IPSS category [27]. Core Lower Urinary Tract Symptom Score (CLSS) questionnaire is more comprehensive than IPSS questionnaire for symptom assessment of men with various diseases/conditions, although both questionnaires can capture LUTS with possible negative impact on QOL [28]. The IPSS alone does not appropriately evaluate female LUTS. The CLSS questionnaire could provide a comprehensive and simple assessment of female LUTS [29].

6.3 Prediction of symptomatic progression
From a systemic review of placebo arm of clinical trials on benign prostatic hyperplasia (BPH), the disease progression was observed in terms of increasing prostate volume and decreased maximal urinary flow rate (Qmax). In addition, the progression increases the risk of acute urinary retention (AUR) and surgery [30]. The community-based and randomized controlled studies identified some clinical parameters which may be associated with clinical progression, complications such as AUR and related surgeries [31–35].
Progression may be associated with higher International Prostate Symptom Score (IPSS), lower Qmax, increased post void residual urine (PVR) and enlarged prostate volume. From the Medical Therapy of Prostatic Symptoms study (MTOPS), the clinical progression of placebo arm (n=737) is 17%, the AUR is 2%, and invasive therapy due to benign prostatic hyperplasia is 5% [36]. The risks for clinical progression in the study may include age ≥62 years old, prostate volume ≥31 mL, prostate specific antigen (PSA) ≥1.6 ng/mL, Qmax <10.6 mL/s and PVR ≥39 mL [37]. However, practicing doctors are faced with patients often representing with several unfavorable conditions not only a single risk. On a systemic analysis of expert opinions, the considerable PVR (>150 mL), poor Qmax (<10 mL/s) and severe symptoms (total IPSS: 20–35) are the most dominant factors predicting an elevated risk of disease progression [38]. Enlarged prostate and high PSA was found to be good clinical predictor of AUR and BPH related surgery [39]. In addition, the high PVR should be reconsidered as a predictor of BPH progression through the interpretation of longitudinal population-based and placebo arm of controlled studies.

6.4 Natural history of BPH after diagnosis

The best way to see the natural history of BPH after diagnosis is to understand the fate of watchful-waiting or placebo treatment group. In a community based longitudinal study which was followed for 12 years showed an average increased IPSS of 0.18 points per year (0.05 for men at 50s to 0.44 at 70s). There was also a decreased Qmax 2% per year and median prostate growth of 1.9% per year. In addition, the accumulative incidence of AUR was 2.7% over 4 years monitoring [40, 41]. In the placebo controlled arm of MTOPS study, the evidence revealed that symptom deterioration (IPSS ≥4 points) was the most prevalent progression event (79.5%), with an accumulative incidence of 14% over a mean follow-up of 4.5 years [36].

From a cohort study in North America, the outcome of men with BPH depends on the initial symptom severity. However, the course of symptoms may vary among patients even with same initial symptom severity [42, 43]. In those who with severe symptoms usually did not have improvement to only mild symptoms. Almost half of patients with moderate symptoms still had moderate symptoms at 4 years follow-up, and eventually a quarter of them underwent surgery.

After the diagnosis of BPH, self-management intervention including lifestyle modification and specific behavioral changes such as decreasing fluid intake at
bed time, avoiding caffeine and alcohol consumption may be the choices of management strategy, and which offer a better clinical response. However, the failure rate at 3, 6 and 12 months is higher in watchful-waiting patients (40.3% vs. 9.6%; 58.2% vs. 17.8%; 65.7% vs. 24.6%) as compared with active management [44]. This evidence indicates the BPH possesses a deteriorated clinical or symptomatic natural history itself and early treatment may be better if patients have bothersome symptoms.
The PROWESS study group revealed that their patients with moderate symptoms have significant greater improvement with finasteride as compared with placebo group. The prostate volume decreased 15.3% in treatment group as compared with placebo group which increased their prostate volume about 8.9% at 24 months [45]. From a nationally representative databases study, in addition to the α blockers therapy, each 30-day delay treatment with 5α-reductase inhibitors may result in an increased overall clinical progression (21.1%), AUR (18.6%) and prostate related surgery (26.7%) within 6 months of follow-up [46]. This means, even under early treatment with α blocker, patients still have a relative higher risk of symptomatic progression if they did not reduce the prostate size. In the Veterans Affairs Cooperative Study, 24% watchful-waiting group patients will undergo surgery within three years waiting assignment [47]. Based on the natural history after diagnosis of BPH either with or without medical treatment, the fact of clinical progression should raise the alertness of clinicians and theses patients should be informed with these facts, especially those who under watchful-waiting treatment.

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7. Pathophysiology of BPH
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BPH is a common disease affecting males above the age of 50 years. It was reported that on autopsy study, 60% of patients above the age of 60 has BPH [1]. It is associated with a significant health impact, either as bothersome lower urinary tract symptoms (LUTS) to patients, or less commonly as potentially serious complications resulting from obstruction to urinary outflow. It may not be easy to distinguish BPH from other lower urinary tract conditions in aging males, since many of their symptoms overlap. Urgency symptoms from detrusor overactivity after chronic obstruction may occur in many BPH patients, but there are just as many BPH patients with bladder decompensation and hypocontractility [2, 3].

The common belief that BPH is a diffused and generalized disease of the prostate, resulting from some form of hormonal derangement that leads to prostatic hyperplasia, enlargement of the overall prostatic size, compression of the prostatic urethra, and a progressive obstruction to the bladder outlet, does not reflect the entire pathophysiology of BPH.

7.1 Pathogenesis
Androgens must be present for prostate cells to grow. While androgens may not directly cause BPH, they play an important permissive role. The observation that castrated pre-pubertal boys do not develop BPH when they age illustrates the presence of androgens is essential for BPH development. The main androgen, testosterone, is converted by 5α reductase to dihydrotestosterone. Dihydrotestosterone is 10-times more potent than testosterone due to its slower dissociation from androgen receptors. Five-alpha reductase inhibitors suppress this enzymatic conversion, resulting in decreased prostatic dihydrotestosterone level, decreased prostatic volume, and symptomatic improvement.

Within the prostate, androgens bind to androgen receptors and initiate the transcription of growth factors that are mitogenic to prostatic epithelial and stromal cells. Such androgenic action can be both autocrine and paracrine in stimulating stromal and epithelial cell growth and differentiation [4–6]. The stromal to epithelial cell ratio is believed to be deranged in BPH. Normally, the ratio is about 2:1, but this increases to more than 3:1 in BPH [7]. The altered
stromal to epithelial interaction leads to the formation of microscopic nodules of fibromuscular hyperplasia. These nodules are first formed in the transition zone just below the smooth muscle collar of the preprostatic sphincter [8]. There are also nodules forming within the periurethral glandular tissue in the smooth muscle collar of the preprostatic sphincter. Within these nodules, fibroblasts transform into smooth muscle cells within a matrix of connective tissues [9]. As these nodules increase in number and size, they coalesce to form larger adenoma. The lateral lobes of BPH are formed from the coalescence of micronodules within the transition zone, whereas the middle lobe of BPH is formed from micronodules within the periurethral sleeve of glandular tissue posteriorly. The remainder of the prostate is then compressed outward to form a false capsule posteriorly [10]. Therefore, BPH is a focal, stromal-induced disease affecting the transition and periurethral zones with formation of fibromuscular micronodules, which increase in size and number and coalesce into the lateral and middle lobes [11].

Being nodular in nature, BPH adenoma can cause obstruction at the bladder outlet and prostatic urethra depending on location, rather than size. A small adenoma sited at the strategic bladder outlet, in the submucosal region can cause significant obstruction, whereas one situated deeper in the stroma of the gland would need to grow to a bigger size before it causes obstruction and symptoms. As in the analogy of the garden hose, it is the distortion which is more important factor that the compression of the prostatic urethra in BPH. Therefore, if the term BPH is reserved for only histological diagnosis, for clinical BPH, it is suggested that the term prostate adenomata (PA) which cause various degree of obstruction would be appropriate. The term benign prostatic enlargement (BPE) to indicate clinical BPH may not be appropriate, for often even when the gland is small and not enlarged by definition, it can still cause significant obstruction when the adenoma is sited at the strategic position causing distortion to urinary flow.

### 7.2 Histopathology
On histological examination, benign prostatic hyperplasia (BPH) contains three main components: 1. Epithelial cells (glandular tissue); it contains acini and ducts. There are three major types of cells: Secretory epithelial cells, basal cells and neuroendocrine cells. Epithelial cells surround the periphery of the acini and secrete into the acini, and then secretions are drained into ducti and urethra. In
the ablation of androgen, there occur a 90% decrease in the number of secretory cells, and an 80% lessening in the volume of cells, 2. Luminal surfaces in acini (glandular lumen), 3. Stroma; stromal tissue composed of smooth muscle, connective tissue, fibroblasts, nerves, lymphatic and blood vessels [12]. The normal adult prostate contains about 20% epithelium, 30% acinar lumens, and 50% stroma according to morphometric studies. As mentioned above, the stromal to epithelial cell ratio is deranged in BPH. Interestingly, it seems that men with symptomatic BPH have a significantly higher proportion of stroma compared to men with asymptomatic BPH. The nature of the predominant nodule in BPH may play a role in determining the patients’ response to treatment. Smooth muscle predominant nodules respond better to alpha antagonists, epithelial nodules to 5α reductase inhibitors, and fibrous nodules to surgery.

The altered stromal to epithelial interaction seems to be mediated by various growth factors. Androgen appears to act via transforming growth factor-alpha (TGF-α) expression to regulate other growth factors, which in turn alter the balance between cell growth and apoptosis within the micronodules. There are five isoforms of TGF-α, of which three are found in mammals (α-1 to α-3), and α-1 and α-2 have been investigated in BPH. TGFα-1 is under a negative feedback by androgen, so a fall in androgen will lead to an increase in TGFα-1 expression [13]. Together with TGFα-2, they are inhibitory on epithelial and stromal cell growth. On the other hand, basic fibroblast growth factor (bFGF) and keratinocyte growth factor (KGF), both are mediated by transforming growth factor-beta (TGF-β) stimulates epithelial and stromal cell growth [14]. Normally, there is a fine balance between the actions of these growth factors. In BPH, the fibroblast growth factors seem to override the transforming growth factors [15]. The eventual formation of the lateral and median lobes distorts the prostatic urethra, and produce bladder outlet obstruction.

7.3 Clinical Pathology

In the clinic, the prostatic adenomata (PA) and the distortion of the bladder neck can be seen with trans-abdominal ultrasound (TAUS) of the prostate and bladder, as intravesical prostatic protrusion (IPP). IPP is the distance measured from the tip of the protruding lobes to the base of the prostate at the circumference of the bladder, seen in the sagittal view on TAUS. A grading system for IPP is well established. Grade 1 IPP is 5mm or less, grade 2 IPP is more than 5mm to
10mm, grade 3 IPP is more than 10mm [16]. Recent studies have shown good correlation between IPP grade and urodynamic evidence of obstruction. It had been found that among patients with grade 1 IPP, only 21% were obstructed; while up to 94% were obstructed among patients with grade 3 IPP [17]. The positive predictive value was 94% and negative predictive value was 79%. In a study comparing IPP and non-invasive Doppler ultrasound urodynamics in diagnosing bladder outlet obstruction noninvasively, IPP was validated to be strongly correlated to obstruction [18]. The sensitivity of the IPP grading was 90% for those with grade 3 IPP and a bladder obstructive Index (BOOI) of more than 40. The specificity for those with grades 1 or 2 IPP, and a BOOI of 40 or less was 60%. Rather than just the overall prostatic volume causing urethral compression and obstruction, IPP also contributes to the degree of obstruction due to urethral distortion by the PA.

Several studies have illustrated the natural history of clinical progression in BPH. The placebo arm of the MTOPS study showed that the risk of clinical progression was 4.5 per 100 man-years, representing a total risk of 17% at 4 years, including symptom deterioration in 14%, retention in 2%, and surgery in 5% [19]. Based on the Olmsted County Study and the Health Professionals Follow-up study, the risk of retention was 6.8/1000 and of surgery was 4.5/1000 respectively [20, 21]. While the natural history of BPH is well established, the challenge is to identify those patients that are likely to deteriorate. In this aspect, IPP grading is a very useful clinical tool. Patients with grade 3 IPP are 7 times more likely to progress than those with grade 1 IPP [22]. IPP also correlates well with other parameters of obstruction in BPH, namely peak urinary flow rate, and prostatic volume [23]. Therefore IPP is a good predictor of disease progression in BPH.

7.4 Clinical Physiology
As the prostate is situated around the bladder neck, PA affect the functions of the bladder first and then the kidneys.

The two basic functions of the bladder are storage and voiding. The storage function can be suspected clinically to be affected if patients developed frequency and urgency with small voided volumes. This can be detected and measured with IPSS, and the voiding dairy, looking at frequency and maximum voided volume (MVV). Storage function can be considered significantly affected if MVV is less than 100ml and deterioration of IPSS by 4 or
The voiding function can be assessed by simple TAUS measurement of the post-void residue urine (PVR). PVR can vary depending on the fluid consumed and the timing of the measurement. However, it can easily be re-measured by asking the patient to pass urine again at the same visit. If necessary, the patient can be asked to return for a subsequent test without the need to drink before the test. Only persistently high PVR would be considered significant.

Obstruction can range from mild to severe. The degree of obstruction can be easily measured by uroflowmetry. Maximum flow rate (Qmax) less than 10mL/s has a 90% correlation with pressure-flow study (PFS) proven obstruction [25]. Poor flow rate can also be due to detrusor dysfunction secondary to a neurogenic cause, diabetes or aging. This can be differentiated by measuring the IPP. Only patients with low grade and poor flow would need to be further investigated with PFS or flexible cystoscopy. For grade 3 IPP, even though the uroflow may be good, more than 12mL/s, 65% were found to be still obstructed on PFS [26].

When would obstruction be considered severe or significant for the clinician to take more active measures? Obstruction would be significant if the functions of the bladder are affected. Thus, when there is persistently high PVR, or poor MVV, then obstruction can be considered clinically significant.

Normal PVR is less than 10mL, what would the cut off for PVR to be considered clinically significant?

**7.5 PVR and UTI:**
A study in 2009 found that among 225 asymptomatic patients, thirty-one percent had a positive urine culture, and they have higher mean PVR of 113mL, compared to 41mL in those without infection (p<0.001) [27]. Another study in 2008 found that among 196 patients without UTI symptoms, 27% had positive urine culture, and their mean PVR was 257mL compared with 133mL in patients with negative cultures. The positive predictive value for bacterial growth at PVR of 180mL or more, was 87% and the negative predictive value was 94.7% [28]

**7.6 PVR and AUR:**
In a community based study of 477 men, it was found that patients with PVR of more than 50mL were 2.5times more common in patient with prostate volume
more than 30mL than those less than 30mL, and also 3 times more likely to have acute urinary retention within 2 to 3 years [29].

In a study of 953 patients from pooled analysis of 11 alfusozin trials, it found that PVR >100mL is statistically related to uroflow, at 60%, 47% and 39% with flow rate of 8mL/s, 8 to 11mL/s and >11mL/s. In the follow up of 1 to 6 months, 7 patients developed acute urinary retention, and 6 out of these 7 patients had PVR of more than 100mL at initial evaluation [30].

There is increasing evidence that dynamic variables such as PVR is important in predicting complication of BPH in community studies and MTOPS. Patients who had AUR had PVR above 100mL in all treatment groups, while those with no AUR their PVR were below 100mL [31].

From the above studies, there is evidence that PVR is an important parameter to assess in patients with BPH, and complications can result from PVR varying from 50 to 180mL. A good cut off of PVR 100mL or more would be appropriate and balanced in our assessment of BPH for further management.

PVR, which is a consequence of infravesical obstruction, is an important predictor of complication of prostatic obstruction. Unlike IPP which is the cause of bladder outlet obstruction, PVR is the consequence of obstruction, and therefore it is inappropriate to use it to predict obstruction. However, it can be used to predict complications from obstruction, like UTI, acute or chronic retention of urine.

**7.7 PVR and Chronic Retention of Urine:**

A more serious complication is chronic retention of urine (CRU). CRU can be defined as a distended painless palpable bladder associated with residual urine >500mL and is often associated with bilateral hydronephrosis. Patients often present with adult onset enuresis and chronic renal failure [32]. Typically, patients do not have lower urinary tract symptoms, and therefore this group of patients would be missed if only IPSS or QOL index are used during management of BPH. A study in 2001 found that among 3277 patients presenting with LUTS, only 0.02% had chronic retention [33]. This may not reflect the true incidence as chronic retention usually do not present with LUTS. As another study from Sri Lanka in Asia in 2004 found 30 patients with chronic retention, within a period of 12 months, presenting with nocturnal enuresis with or without hydronephrosis [34].
7.8 Assessing Symptoms:
Thus, there are strong evidences that many BPH patients can have significant obstruction with minimum urinary symptoms, and yet, suffer from serious complications such as high pressure chronic retention, bilateral hydronephrosis and renal impairment. The International Prostate symptoms Score (IPSS) and the quality of life score (QOL) has only weak correlation with the degree of obstruction and therefore should not be used alone in the management of BPH.

7.9 Symptoms and Obstruction
Siris et al 1996 in a study of 75 men with “prostatism” and correlating with Qmax, PVR and PFS found 33 men with severe symptoms and 42 men with mild or moderate symptoms, 40 men had obstruction and 35 had equivocal or no obstruction. The sensitivity and specificity of AUA symptoms index (precursor of IPSS) for PFS definition of obstruction was 42.5% and 54.3%, the conclusion was that symptoms score should not be used to gauge the degree of obstruction [35].
Bosch JL et al 1995, in a study of community based subjects found 12% with zero IPSS but 82% claimed to have “no voiding complain”. There was weak co-relation between IPSS with PV (r=0.19), Qmax (r=-0.18) and PVR (r=0.25).The study concluded that the parameters in BPH should be considered independently and that IPSS should not be used as a pre-selection criterion in the determination of the prevalence of clinical BPH [36].
Wadie BS et al 2001 studied 460 men, and correlated the IPSS with PV, Qmax, PVR and PFS and found no correlation with the total, obstructive or irritative symptoms. They concluded that symptoms scores are qualitative and to use them to quantify the degree of obstruction or evaluate therapy was questionable [37].
Rosier PFWM et al 1996, in a study of 707 with LUTS, also found no co-relation of IPSS with obstruction, patients with mild symptoms (0–7), 51% were still obstructed, while those with severe symptoms 37% were not obstructed [38].
Chia SJ et al (2003) in a study of 200 patients with LUTS found that severe IPSS (21–35), 57% were obstructed, while those with IPP more than 10mm (Grade3), 94% of patients were obstructed [17]. Lim LS et al (2010) also showed that there is no correlation between severity of IPSS and IPP [22].
Using IPSS and QOL solely to decide on further management is too simplistic
and this would lead to overtreatment and under treatment in some patients. BPH as a clinical entity (clinical BPH) is a composite of the gland causing obstruction and symptoms (Hald Diagram) [39]. Therefore all three components should be included in the total holistic assessment of the patient with clinical BPH. The global QOL is more important than the total IPSS. This is because if the patient is not bothered by his symptoms, there may not be a need to treat him, unless he has significant obstruction by the prostate gland. Deterioration of IPSS by 4 or more points may be important in the follow up of patients as it may suggest the development of detrusor instability or over active bladder (OAB) as a result of progression of BPO.

7.10 Application of Pathophysiology to clinical Practice in Real Life

Therefore for further management of BPH, significant obstruction as defined above with persistent PVR of >100mL, should be ruled out first before considering symptoms. Basic principle is that treatment should be according to the severity of the disease. The cause of the obstruction and symptoms is the prostate adenoma (PA). However, it is not necessary to treat all patients just because the adenoma is there. IPP is useful in diagnosing the adenoma and the degree of IPP predicts obstruction and progression of the disease. Though IPP predicts that 49% of patients with grade 3 IPP will deteriorate, 51% still do not deteriorate with a mean follow up of 30 months [22]. Treating patients just because he has a grade 3 IPP would lead to over treatment of this cohort of patient. Therefore, treatment should take into account whether the PA has resulted in significant obstruction and bothersome symptoms, that is according to the severity of the disease.

7.11 Staging of BPH

The severity of the disease BPH can be classified according to the stage, combining the presence or absence of significant obstruction or bothersome symptoms [40]. As discussed above, persistent PVR >100mL can be used as a cut off to define significant obstruction, which should prompt the clinician to take more active action in the management of BPH. In real life practice, PVR varies according to the amount of pre-micturition volume and the timing of performing the measurement; therefore it is emphasized that the PVR must be persistent. Thus if patient has PVR >100mL, he is asked to void again and measurement retaken. Also the PVR is interpreted together with the Qmax which is generally
below 10mL/s and high grade IPP. Thus clinical BPH can be classified as;
Stage I: patients with No Significant Obstruction and No Bothersome symptoms
Stage II: patients with No Significant Obstruction but has Bothersome symptoms
(Defined as QOL ≥3)
Stage III: patients with Significant Obstruction defined as persistent PVR>100mL
or MVV (maximum voided volume) less than 100mL, irrespective of symptoms.
Patients may have more irritative symptoms because of inability to store, or no
bothersome symptoms in spite of large residue urine which would lead to chronic
retention of Urine and UTI.
Stage IV: patients with acute retention of urine, chronic retention, bladder stones,
recurrent UTI and hematuria.
As in malignant disease, further management of clinical BPH would be
according to the grade and stage of the disease.
Stage I,Grade 1 can generally be watch, Stage III, grade3 would need more
aggressive treatment with pharmacotherapy such as combined α blocker with
5α-reductase inhibitors, or option for surgery, depending on the patients general
well-being, age and preferences. Stage IV high grade prostate would need
surgery. Generally there is good concordance between the grade and stage, but
if there is discordance with high stage low grade prostate as seen in about 16%
(7/44) of our patients then further more invasive investigations with urodynamic
studies and or flexible cystoscopy are indicated.
With this classification, of 406 patients 59% of patients can be watched, 32%
treated with pharmacotherapy and 9% had surgery at initial evaluation [41]. In an
Asian study by MK Li, of 892 patients, 17% were watch, 72.8% had
pharmacotherapy and 10.2% had surgery [42].

Conclusion
With better understanding of the pathophysiology of clinical BPH, patients can
be diagnosed clinically with non-invasive ultrasound and classified according to
grade and stage. The grade predicts the obstruction and progression, while the
stage guide the treatment. This staging system for BPH disease severity is
proposed in the initial UAA Guideline, but is not widely accepted, nor
recommended in the Guidelines of EAU, or AUA, or JUA, yet.
The final choice would take into account patients age, co-morbidity and his
preferences. Treating the patients as a whole would lead to a more balanced
and cost effective management and this is especially so in our Asian region.
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8. Complications of BPH
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Many of the complications of progressive BPH are rare, and much of the knowledge comes from studies of men presenting with such complications for treatment (i.e., cases) rather than observing cohorts of men for the development of complications. Severe symptoms, urinary retention, gross hematuria, recurrent urinary tract infections, bladder calculi, and hydronephrosis or renal insufficiency warrant transurethral incision, resection, vaporization, or open prostatectomy (for very large neoplasms).

8.1 Mortality
Levi et al. have considered trends in mortality from BPH over the last decades in Europe and, for comparative purposes, the USA and Japan. Between the early 1950s and the late 1990s, overall mortality from BPH in the European Union (EU) fell from 5.9 to 3.5 per million, and the decline since the late 1950s was over 96%. Comparable falls were observed in the USA and Japan, and BPH mortality rates in the late 1990s were lower than in the EU (1.8/10^6 in the USA, 1.4 in Japan) [1, 2]. In the 1950s, death rates from BPH in the few Asian countries that provided data were low on a worldwide scale (3-6/100 000 in Hong Kong, 1-2 in Japan, and 1-7 in Singapore). Substantial reductions were observed nonetheless over the last few decades, and rates in the late 1980s or early 1990s were around 0-2/100 000 in these countries (three of the lowest rates in the world). The reductions were observed in various age groups, but were larger at younger ages [2, 3]. If the mortality rates from 1950 were applied to 1990, 13,681 fewer deaths occurred in the United States alone than expected, a major but unheralded health care achievement. The most probable interpretation of these trends is that therapeutic improvements—including more widespread and timely surgery, introduction of less invasive techniques, such as transurethral prostatectomy, and possibly the development of medical treatments—have had a favorable and substantial impact on BPH mortality. There are, however, areas of the world, including several countries of Western Europe and South America, where rates are still very high [4].
8.2 Acute Urinary Retention
Acute urinary retention (AUR) is, for several reasons, one of the most significant complications or long-term outcomes resulting from BPH. The epidemiology of AUR is better understood in recent years and it has even been demonstrated from randomized trials that, probably, a portion of AURs can be prevented [5]. An AUR can occur spontaneously (that is without any external triggering event) or can be provoked by triggers like general or regional anesthesia, non-prostate-related surgery, transurethral instrumentation, certain medications that have an effect on lower urinary tract function, excessive fluid (particularly alcohol) intake and sexual activity. In older studies of the occurrence of AUR the range of the incidence rates has varied widely between 4 and 130 per 1000 person-years [6]. In more recent studies, rates range from about 2 to 18 per 1000 person-years. It has in the past represented an immediate indication for surgery. For this reason alone, AUR is both from an economic viewpoint as well as from the viewpoint of the patient, an important and feared event, but, the etiology of AUR is poorly understood. From a clinical and prognostic point of view, spontaneous AUR should be separated from precipitated AUR, latter of which refers to the inability to urinate after a triggering event such as non–prostate-related surgery, catheterization, anesthesia, ingestion of medications with sympathomimetic or anticholinergic effects or antihistamines, or others. All other AUR episodes are classified as spontaneous [7]. The importance of differentiating the two types of AUR becomes clear when evaluating the ultimate outcomes of patients. After spontaneous AUR, 15% of patients had another episode of spontaneous AUR and a total of 75% underwent surgery, whereas after precipitated AUR only 9% had an episode of spontaneous AUR, and 26% underwent surgery [7]. Since 49% of AUR cases amongst the LUTS/BPH patients presented with AUR as the first symptom, i.e. without previous contacts with a health care provider, it is clear that earlier patient identification is needed if we aim to reduce the incidence of AUR by means of pharmacological treatment [8]. Presently this type of risk assessment is only possible in men who have seen a health care provider for an assessment.

8.3 Bladder Stones
The mechanism for bladder stone formation with BPH may the congestion of urine (post-void residual urine). In a large autopsy study the prevalence of bladder stones was 8 times higher in men with a histologic diagnosis of BPH
(3.4%) compared with controls (0.4%) but no increased incidence of ureteral or
kidney stones were found [9]. Recurrence rate of stones after removal without
BPH surgery has been reported as 17.4% [10].
In a study comparing watchful waiting and TURP in men with moderate
symptoms, only 1 of 276 patients assigned to watchful waiting developed a
bladder stone in 3 years of follow-up [11]. The self-reported rate of a bladder
stone in a cross-sectional study in 2002 Spanish men was 0.7% [12] In clinical
practice the risk of bladder stone development is small and screening only
indicated if clinical circumstances warrant it (e.g., hematuria, stuttering of
urination).

8.4 Recurrent Urinary Tract Infections
The mechanisms of recurrent UTI in BPH are believed to be increased post-void
urine volume, and in case of urinary retention, urethral catheterization, however,
clear evidence is lacking. As the previous statement, surgical treatment is
generally reserved for those patients [13]. In older surgical series UTIs constitute
the main indication for surgical intervention in about 12% [14, 15]. The incidence
of UTIs in the placebo-treated patients was only 0.1/100 patient-years in the
MTOPs study [16].

8.5 Decompensated bladder
Irreversible loss of bladder (voiding) function sometimes occur in BPH patients.
However, when the process starts, whether it really is related to BPH and
obstruction, and when an intervention is necessary to prevent decompensating
with resultant inability to void is unclear. Decompensated bladder, or impaired
detrusor contractility may also occur as normal consequence of aging [17].
The critical question is whether delayed intervention might lead to progressive
irreversible loss of bladder function and misses a window for cure. There is no
direct evidence for this from longitudinal population or clinic patient studies.
However, one report with randomized comparison between initial TURP and
delayed TURP with initial conservative treatment showed that the conservative
arm to TURP later in the trial had not as significant an improvement in symptoms
and flow rate compared with those who underwent TURP at the beginning after
randomization [18].

8.6 Upper Urinary Tract Deterioration and Azotemia
In general, the incidence of end stage renal failure in patients with BPH is rare (lower than 1%), however, several guidelines recommend measurement of serum creatinine as an initial evaluation [19]. BPH patients with renal impairment often are complicated with DM or hypertension [20]. The Agency for Health Care Policy and Research BPH guidelines reported a mean of 13.6% (range 0.3% to 30%) of patients presenting for TURP with evidence of renal failure based on predominantly older studies. In the large database of patients who had upper tract imaging before surgery, 7.6% of 6102 patients in 25 series had evidence of hydronephrosis, of whom one third had renal insufficiency [21].

8.7 Hematuria
In BPH patients who have been indicated to surgery, 12% showed macroscopic hematuria [22]. It has always been recognized that patients with BPH might develop gross hematuria and form clots with no other cause being identifiable. One of the reasons may be upregulation of vascular endothelial growth factor (VEGF) and increase in the density of microvessel density [23–25]. Precise population estimates and incidence rates are not available, and the clinical management is dictated by the circumstances.

References


9. Diagnosis & Investigation for BPH/Male LUTS
Rohan Malek, M.D., and Selvalingam Sothilingam, M.D.

Diagnosis of LUTS due to BPH should be considered in males above the age of 45 years presenting with lower urinary symptoms especially in the presence of demonstrable enlargement of the prostate (BPE). Patients with lower urinary tract symptoms suggestive of BPH seek medical advice because they are bothered by their urinary symptoms [1, 2]. Patients may also present with bladder outlet obstruction (BOO) at the first presentation. In Asia where symptomatic patients may present late in the course of their disease, many of them may present with complications from BPH such as hematuria, urinary tract infection, urinary stones, renal failure and acute or chronic urinary retention. Difficulties in translation of BPH guidelines into clinical practice are related to lack of knowledge, differences in routine practices, beliefs, cost, availability and reimbursement policies [3, 4]. Therefore the diagnosis and investigation of BPH in Asia should take into account the wide variability of the socio economic situation and the differing medical practices in Asian countries. It is understandable that not all patients with LUTS would have access to urologists or to centers with urological facilities, therefore these guidelines have been formulated taking into account the minimum investigations that should be done even at the level of the primary healthcare provider or general practitioner. There are significant differences in the practice patterns between primary care physicians and urologist in the evaluation of BPH [5].

9.1 Conditions not suitable for general physicians
It is recommended that patients seen by primary care physicians should be referred to the urologist in the presence of the following: (Level IV evidence, Grade C recommendation) [3, 6].

9.1.1 Urinary Retention
9.1.2 Palpable bladder
9.1.3 Urinary Incontinence
9.1.4 Hematuria
9.1.5 Proven urinary tract infection
9.1.6 Persistent bothersomeness
9.1.7 Bladder Stones
9.1.8 Hard Prostate
9.1.9 PSA > 4 ng/mL (> 2 ng/mL, pts on 5ARI [7])

We propose that for Asia, investigations should be categorized as

9.2 Highly recommended (All Medical Practitioners)
9.3 Recommended in special settings (Urologist, Urological Centers)
9.4 Optional

All tests included in the highly recommended category are also recommended by AUA, EUA, BAUS, 5th International Consultation on BPH, Australian NHMRC and JUA [8–13].

9.2 Highly Recommended Tests

9.2.1 Medical history should be thorough taking into account duration, severity of lower urinary tract symptoms and mandatory to include history of incontinence and hematuria [14]. History should also take into consideration patients’ general condition including neurologic and, psychiatric disorders, diabetes mellitus and cardiac diseases. History of bowel habit is relevant and so is patient’s mobility and social support. Important drug history should include use of diuretics, antiplatelet/anticoagulants and antihypertensives. Previous urinary tract intervention or urethral trauma should also be questioned. Family history is equally important especially of prostate disease or prostate cancer. Patients should also be questioned on erectile dysfunction.

9.2.2 Physical Examination includes general examination including assessment of blood pressure and must include digital rectal examination [15], neurological examination especially of the lower extremities and anal sphincter tone. The digital rectal examination should comment on estimated prostate volume, prostate surface and consistency. Lower abdominal examination to look for palpable bladder should also be performed. Examination of genitalia is equally important.

9.2.3 Symptom Scores would be useful and the International Prostate Symptom Score (IPSS) is most commonly used [14]. However it should be validated according to the spoken and written language(s) of the respective Asian countries. Using the IPSS symptom score, patients can be categorized as having predominant voiding, storage or post micturition symptoms [16]. This can guide in choosing therapeutic options and in follow up of patients after treatment. QOL symptom score is useful to assess the bothersomeness of the LUTS. In patients with significant storage symptoms, additional symptoms scores such as
the OAB symptom score (OABSS) may be useful [12].

9.2.4 Urinalysis is recommended [17] to detect microscopic hematuria and pyuria to exclude other urological conditions that can cause LUTS such as urinary infection, urological malignancies and urinary stones [18].

9.2.5 Serum Creatinine, although not recommended in AUA, is recommended here as initial assessment. In the context of the high incidence of diabetes mellitus and stone disease in Asia, the rate of silent renal insufficiency is expected to be high. This is more so in countries where access to medical facilities is not readily available.

9.2.6 PSA is recommended in patients with more than 10 years life expectancy or in patients in whom PSA will make a difference in management of the prostate disease [4, 13]. Patients should be counseled adequately prior to performing the PSA test. A baseline PSA would be useful in predicting patient’s 10 or 15 year risk of prostate cancer based on evidence from current literature. There is evidently a relationship between PSA and prostate volume [19, 20]. Therefore PSA can also be used as a guide on identifying patients at risk for BPH progression [21, 15].

9.2.7 Bladder diary is recommended in patients with predominantly storage symptoms and in patients where nocturia appears to be most bothersome [22, 23], to exclude nocturnal polyuria.

9.3 Recommended in Special Settings

9.3.1 Uroflowmetry, where facilities are available can be done to assess Qmax where a Qmax <10 mL/s may indicate a stronger need for surgical intervention [24]. At least two readings would be preferable and the voided volume should be more than 150 mL [25]. Furthermore a flat pattern on uroflowmetry may alert the physician on the possibility of urethral stricture disease.

9.3.2 Post Void Residual (PVR) urine is recommended after having done a uroflowmetry. Although there is intra individual variations in the values and problems in reproducibility, a high PVR may indicate bladder dysfunction and poorer response to medical therapy [26] although there is no consensus on the cutoff point [27].

9.3.3 Prostate Ultrasound either transabdominal or transrectal, is recommended where facilities are available, in symptomatic patients to assess prostate size and presence of Intravesical Prostatic Protrusion (IPP) to help
decide on the most appropriate management for the patient [28, 29]. Patients with IPP Grade 3 would be suitable candidates for surgical intervention [29]. It may also be useful to assess very large prostates when considering open prostatectomy.

9.4 Optional

9.4.1 Upper Tract Imaging is recommended when there is microscopic or macroscopic hematuria, renal insufficiency, in patients with chronic retention or in patients with stone disease [18]. KUB X ray may routinely be done in countries where stone disease is endemic.

9.4.2 Urodynamics can be performed for specific indication, i.e. in the very young (< 50yrs) or old (> 80 yrs.) patients with LUTS [18], symptomatic patients with Qmax >15 mL/s, patients with large PVR with no significant IPP, patients suspected of having neurogenic bladder or after radical pelvic surgery and in patients who have had surgery for BPH but are still symptomatic.

9.4.3 Transrectal Ultrasound biopsy of prostate is recommended for indicated patients with PSA> 4ng/ml and or in those with suspicious DRE findings where prostate cancer is suspected.

9.4.4. Cystoscopy is recommended in patients with hematuria, suspected urethral stricture, before surgery, in patients who had prior lower tract surgery or in BPH patients not responding to medical treatment [18]. Urine cytology is recommended in patients with hematuria or in BPH patients not responding to medical treatment.

9.4.5 Retrograde Cystourethrogram may be done in patients with history and uroflow assessment suggestive of urethral stricture to provide further information on length and site of urethral stricture.

References

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10. Recommended grade for treatment: Pharmacotherapy and Conservative Management
Kyu-Sung Lee, M.D., Joon Chul Kim, M.D.

10.1 Pharmacotherapy
Drugs used for the treatment of various forms of male LUTS are listed in Table 1. The level of evidence and the grade of recommendation (according to the current classification) for each drug treatment are summarized in Table 2.

Table 1. Key pharmacokinetic properties and standard doses of drugs in Asia for the treatment of male LUTS.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tmax (hours)</th>
<th>T½ (hours)</th>
<th>Recommended daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfuzosin IR</td>
<td>1.5</td>
<td>4–6</td>
<td>3 x 2.5 mg</td>
</tr>
<tr>
<td>Alfuzosin SR</td>
<td>3</td>
<td>8</td>
<td>2 x 5 mg</td>
</tr>
<tr>
<td>Alfuzosin XL</td>
<td>9</td>
<td>11</td>
<td>1 x 10 mg</td>
</tr>
<tr>
<td>Doxazosin IR</td>
<td>2–3</td>
<td>20</td>
<td>1 x 2–8 mg</td>
</tr>
<tr>
<td>Doxazosin GITS</td>
<td>8–12</td>
<td>20</td>
<td>1 x 4–8 mg</td>
</tr>
<tr>
<td>Naftopidil</td>
<td>2.2</td>
<td>13.2</td>
<td>1 x 25–75 mg</td>
</tr>
<tr>
<td>Silodosin</td>
<td>2.5</td>
<td>11–18</td>
<td>2 x 4mg, 1 x 8 mg</td>
</tr>
<tr>
<td>Tamsulosin MR</td>
<td>6</td>
<td>10–13</td>
<td>1 x 0.2–0.4 mg</td>
</tr>
<tr>
<td>Tamsulosin OCAS</td>
<td>4–6</td>
<td>14–15</td>
<td>1 x 0.4 mg (1x0.2mg in Japan)</td>
</tr>
<tr>
<td>Terazosin</td>
<td>1–2</td>
<td>8–14</td>
<td>1 x 2, 5, 10 mg</td>
</tr>
</tbody>
</table>

| 5α-reductase inhibitors (for treating benign prostatic enlargement due to BPH) |

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tmax (hours)</th>
<th>T½ (weeks)</th>
<th>Recommended daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutasteride</td>
<td>1–3</td>
<td>3–5 weeks</td>
<td>1 x 0.5mg</td>
</tr>
<tr>
<td>Finasteride</td>
<td>2</td>
<td>6–8 hours</td>
<td>1 x 5 mg</td>
</tr>
</tbody>
</table>

| Anticholinergic drugs (for treating overactive bladder/storage symptoms) |

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tmax (hours)</th>
<th>T½ (hours)</th>
<th>Recommended daily dose</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Drug treatment</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. α1 blockers should be offered to men with moderate-to-severe lower urinary tract symptoms.</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Long-term treatment with α1 blockers for BPH patients is effective bot</td>
<td>1</td>
<td>A</td>
</tr>
</tbody>
</table>

Table 2. Level of Evidence (LE) and Grade of Recommendation (GR) of drug treatments of male LUTS

- 99 -
h subjectively and objectively.

<table>
<thead>
<tr>
<th></th>
<th>2. 5α-reductase inhibitors are appropriate and effective treatment alternatives for men with LUTS secondary to BPH who have demonstrable prostate enlargement. 5α-reductase inhibitors can prevent disease progression with regard to acute urinary retention and need for surgery. The treatment is not recommended for short-term therapy (&lt;1 year). Long-term treatment with 5α-reductase inhibitors is effective and well tolerated.</th>
<th>1</th>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 Anticholinergics might be considered in men with moderate to severe lower urinary tract symptoms who have predominantly bladder storage symptoms with or without α1 blockers. Caution is advised in men with increased postvoid residual urine volume.</td>
<td>1</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>4. PDE5 inhibitors reduce moderate to severe male lower urinary tract symptoms.</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>5. Desmopressin can be used for the treatment of nocturia secondary to nocturnal polyuria. Caution is advised in old men with hyponatremia and impaired renal function. Serum sodium concentration level should be monitored periodically.</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>6 Plant extracts reduce moderate to severe male lower urinary tract symptoms. Although plant extracts agents show some promise for symptom relief, their use remains controversial due to the lack of established mechanisms of action, efficacy, and safety. Clinical trials are often flawed, as most studies of small scale and short duration are; they are not blinded or controlled, and most have no placebo group.</td>
<td>3</td>
<td>C2</td>
</tr>
<tr>
<td></td>
<td>7 Combination treatment with α1 blocker together with 5α-reductase inhibitor should be offered to men with moderate-to-severe lower urinary tract symptoms, enlarged prostates (≥30 mL or ≥40 mL), and reduced Qmax (men likely to develop disease progression). Combination treatment is not recommended for short-term therapy (&lt;1 year).</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>8. Combination treatment with α1 blocker and anticholinergic might be</td>
<td>1</td>
<td>B</td>
</tr>
</tbody>
</table>
considered in patients with moderate to severe lower urinary tract symptoms if symptom relief has been insufficient with the monotherapy of either drug.

Combination treatment should cautiously be prescribed in men who are suspicious of having bladder outlet obstruction with increased postvoid residual urine volume.

| 2 | B |

The combination of α1 blocker and PDE 5 inhibitor is well tolerated and effective in improving lower urinary tract symptoms. However caution is advised in men with hypotension.

| 2 | A |

Intra-prostatic botulinum toxin injections for lower urinary tract symptoms due to benign prostatic obstruction or urinary retention are still experimental. Intra-prostatic botulinum toxin injections should be performed only in clinical trials.

| 3 | C |

### 10.1.1 α1 adrenergic receptor antagonists (α1 blocker)

Alpha1-blockers produce a significant symptom improvement compared to placebo, which the average patient will appreciate as a moderate improvement from baseline [1-4]. The minor differences in efficacy noted between the different α1 blockers are not statistically (when tested) or clinically significant [5]. Prostate size does not affect α1 blocker efficacy but patients with smaller prostates (<40 mL) seem to have better efficacy compared to those with larger glands [6]. α1 blockers do not reduce prostate size and do not prevent acute urinary retention, so that eventually some patients will have to be surgically treated [7]. Nevertheless, the efficacy of α1 blockers appears to be maintained over at least 4 years [8]. The most frequent side-effects of α1 blockers are asthenia, dizziness and (orthostatic) hypotension [9]. Although a reduction in blood pressure may benefit hypertensive patients, at least some of the observed asthenia and dizziness can be attributed to a decrease in blood pressure [10,11].

A systematic review concluded that α1 blockers do not adversely affect libido, have a small beneficial effect on erectile function, but sometimes cause abnormal ejaculation [12].

Originally, the abnormal ejaculation was thought to be retrograde, but more recent data demonstrate that it is due to emission failure [13-20]. Although abnormal ejaculation has been observed more frequently with
tamsulosin [21-25], the apparently greater risk for abnormal ejaculation with tamsulosin is intriguing as even more α1A-selective drugs, silodosin, carry a greater risk [26-28].

References


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10.1.2 5α-reductase inhibitor (5ARI)

5α-reductase inhibitors (Finasteride inhibits type 1 only, Dutasteride inhibits both type 1 and 2) reduce LUTS (IPSS; moderate to severe) by approximately 15–30%, decrease prostate volume by approximately 18–28% and increase Qmax of free uroflowmetry by approximately 1.5–2.0 mL/s in patients with LUTS due to prostate enlargement [1-8]. 5ARIs, but not α1 blockers, reduce the long-term
(>1 year) risk of acute urinary retention or need for surgery [9-12].

The most relevant adverse effects of 5ARIs are related to sexual function and include reduced libido, erectile dysfunction and, less frequently, ejaculation disorders. The incidence of sexual dysfunction and other adverse events is low and even decreased with trial duration [3].

5ARIs should not be used in men with LUTS secondary to BPH without prostatic enlargement. Due to the slow onset of action, 5ARIs are only suitable for long-term treatment (many years) [13-15].

Their effect on the serum PSA concentration needs to be considered for prostate cancer screening.

Of interest, 5ARIs might reduce blood loss during transurethral prostate surgery, probably due to their effects on prostatic vascularization [16].

Long-time use of 5ARIs can improve urodynamic parameters [17-18].

References


10.1.3 Anticholinergics
Muscarinic freceptor subtypes, especially M3 is the most important for urinary bladder detrusor function [1-5], and muscarinic receptor antagonists are valuable treatment modality for overactive bladder [6,7]. For elderly population, there are higher incidence of adverse events than younger [8]. Anticholinergics might be considered in men with moderate to severe lower urinary tract symptoms who have predominantly bladder storage symptoms, however, potential risk for urinary retention is a concern withoutα1 blockers [9-16]. Hence, combination treatments or α1 blocker add-on treatments have been evaluated [17-20]. Especially it may benefit men with lower PSA levels (smaller prostates) [21].

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Group: Solifenacin as add-on therapy for overactive bladder symptoms-
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Effects of serum PSA on efficacy of tolterodine extended release with or 
without tamsulosin in men with LUTS, including OAB. Urology 2008; 72: 
1061–7.

10.1.4 PDE5 inhibitor
Nitric oxide/cyclic GMP pathway is an important functional implication not 
only in penile erectile function, but in prostate/bladder neck smooth muscle 
function [1-5]. Further study revealed that phosphodiesterase (PDE) isoenzy 
mes are present in the lower urinary tract and prostate in human [6, 7]. 
PDE5 inhibitors may well have a role in therapy for BPH/LUTS, for either of 
LUTS or uroflow [8-14]. Among PDE5 inhibitors initially developed for 
erectile dysfunction, tadalafil has been shown to be effective for Male/LUTS 
in USA, European countries, and Asia [15-21]. It is likely that PDE5 inhibitor treatment will be of value, especially for men with 
LUTS and significant ED [22-24]. Other PDE5 inhibitors have been tried for 
Male LUTS/BPH [25].

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10.1.5 Desmopressin
Desmopressin acetate (desmopressin) is a synthetic analogue of AVP (AVP: arginine vasopressin) with high V2 receptor affinity and antidiuretic properties. It is the only registered drug for antidiuretic treatment. In contrast to AVP, desmopressin has no relevant V1 receptor affinity and hypertensive effects [1,2]. The clinical effects - in terms of urine volume decrease and an increase in urine osmolality - last for approximately 8-12 hours[2]. Desmopressin may be used by intravenous infusion, nasal spray, tablet, or MELT formulation [3,4]. Desmopressin significantly reduced nocturnal diuresis, decreased the number of nocturnal voids, and extended the time until the first nocturnal void [5-7]. The 24-hour diuresis remained unchanged during desmopressin treatment. Desmopressin should be taken once daily before sleeping [8]. As the optimal dose differs between patients, desmopressin treatment should be initiated at a low dose (0.1 mg/day) and may be gradually increased every week until maximum efficacy is reached [9]. For elderly patients, efficacy and safety have been shown [9-12], however, the most frequent adverse events were headache, nausea, diarrhea, abdominal pain, dizziness, dry mouth, and hyponatremia. Hyponatremia was observed mainly in patients aged 65 years[13-16]. Caution is advised in old men with hyponatremia and impaired renal function. Serum sodium concentration level should be monitored periodically.
References


10.1.6 Plant extract/Herbal medicine

Phytotherapy comprises the medical use of various extracts of different plants. The most important compounds are believed to be phytosterols, β-sitosterol, fatty acids, and lectins[1]. In vitro studies have shown that plant extracts have so many functions. They have anti-inflammatory, anti-androgenic, oestrogenic effects, decrease sexual hormone binding globulin (SHBG), inhibit aromatase, lipoxy-genase, growth-factor stimulated proliferation of prostatic cells, α1-adrenoceptors, 5 α-reductase, muscarinic cholinceptors, dihydropyridine receptors, or vanilloid receptors, and improve detrusor function, neutralise free radicals [1-3]. In spite of a lot of mechanisms of action, phytotherapy remains problematic to use because of different concentrations of the active ingredient(s) in different brands of the same phytotherapeutic agent [4,5]. Although plant extracts agents show some promise for symptom relief, their use remains controversial due to the lack of established mechanisms of action, efficacy, and safety [6-13]. Clinical trials are often flawed, as most studies are of small scale and short Duration. They are not blinded or controlled, and most have no placebo group.
Hence, meta-analyses of extracts of the same plant do not seem to be justified and results of these analyses have to be interpreted with caution.

References


10.1.7 Combination treatment with α1 blocker and 5α-reductase inhibitor

Several studies have investigated the efficacy of combination therapy against the efficacy of an α1-blockers and 5α-reductase inhibitors, or placebo alone. Initial studies with follow-up periods between 6 and 12 months used symptom (IPSS) change as their primary endpoint [1-3]. All of these trials demonstrated that the α1-blocker was superior to finasteride in symptom reduction, whereas the combination treatment was not superior to the α1-blocker alone. More recently, 4-year data analysis from MTOPS (medical therapy of prostatic symptoms) as well as the 2- and 4-year results from the CombAT (Combination of Avodart® and Tamsulosin) trials, have been reported [4-6].

In contrast to earlier studies with only 6 to 12 months follow-up, long-term data have demonstrated that combination treatment is superior to either monotherapy with regard to symptom reduction and Qmax (maximum urinary flow rate during free uroflowmetry) improvement and superior to α 1-blocker in reducing the risk of acute urinary retention and the need for surgery [4-6].

Regarding discontinuation of α1 blockes after long-term combination therapy, almost three-quarters of patients reported no worsening of symptoms. However, patients with severe symptoms (IPSS > 20) at baseline may benefit from longer combination therapy [7]. LUTS after discontinuation of α1 blocker was sustained at 3 months (IPSS difference 1.24) and 9 months (IPSS difference -0.44) [8]. Dutasteride patients discontinued α 1-blocker therapy 64% faster than finasteride patients at any time point [9].

Combination therapy should only be used when long-term treatment (more than 12 months) is intended. Combination therapy with α1 blocker and
5α-reductase inhibitor should be used primarily in men who have moderate to severe LUTS and are at risk of disease progression (higher prostate volume, higher PSA concentration, advanced age, etc.). The adverse events observed during combination treatment were typical of an α1 blocker and 5ARI. The frequencies of adverse events were significantly higher for combination therapy for most adverse events.

References

**10.1.8 Combination treatment with α1 blocker and anticholinergic**

Combination treatment with α1 blocker and anticholinergic might be considered in patients with moderate to severe LUTS if symptom relief has been insufficient with the monotherapy of either drug.

At least nine trials have been published investigating the efficacy of the combination treatment with α1-blockers and muscarinic receptor antagonists in adult male patients with LUTS LUTS: lower urinary tract symptoms [1-8]. These trials demonstrated that persistent LUTS can be significantly reduced by the additional use of a muscarinic receptor antagonist especially if detrusor overactivity had been demonstrated [1-8]. Patient reported QoL, treatment benefit, symptom bother, or patient perception of bladder condition was significantly improved in the combination treatment arm [9-13]. The combination treatment significantly reduced urgency urinary incontinence episodes as well as urgency and significantly increased QoL compared to α1 blockers or placebo alone. Combination treatment should cautiously be prescribed in men who are suspicious of having bladder outlet obstruction with increased postvoid residual urine volume [13-15].

**References**


3. Lee KS, Choo MS, Kim DY et al. Combination treatment with propiverine hydrochloride plus doxazosin controlled release gastrointestinal therapeutic system formulation for overactive bladder coexisting benign


### 10.1.9 Combination treatment with α1 blocker and PDE 5 inhibitor

The combination of α1 blocker and PDE 5 inhibitor is well tolerated and effective in improving lower urinary tract symptoms [1-4]. However caution is advised in men with hypotention. Further data on safety and cost-effectiveness, especially for combination therapy, will be needed.

**References**


10.1.10 Botulinum toxin (BTX-A)

BTX-A inhibits vesicular neurotransmitter transport from nerve terminal via inhibition of SNAIR/SNAP proteins [1]. Two commercially available products (Botox™, Dysport™) of type A Botulinum toxin are now available in USA and European countries (Table 1). The possible mechanisms of the effect of intraprostatic injection of BTX-A may be variable including apoptosis [2-5]. In addition to initial short term effects on the small prostate [6-8], long-term effects on LUTS, prostate volume, and QOL, were evaluated [9-14]. There are some evidences to support its efficacy [9-14], large volume RCT data is lacking [15,16]. Intra-prostatic BTX injections for LUTS due to benign prostatic obstruction or urinary retention are still experimental.

References


10.1.11 \( \beta_3 \)-Adrenoceptor agonist, Mirabegron
A β3-Adrenoceptor agonist, Mirabegron, alleviates symptoms of OAB while having a mechanism of action that provides an alternative for patients who are intolerant of or who have contraindications to anticholinergic agents [1]. The place in therapy of mirabegron relative to anticholinergics in the treatment of OAB secondary to BPH has not yet been established[2], however, urodynamic safety for BPH/BOO has been confirmed[3].

References
2. Otsuki H, Kosaka T, Nakamura K, Mishima J, Kuwahara Y, Tsukamoto T: β3-Adrenoceptor agonist mirabegron is effective for overactive bladder that is unresponsive to antimuscarinic treatment or is related to benign prostatic hyperplasia in men, 2013;45:53-60.
10.2 Conservative Therapy

In this chapter, conservative therapies including lifestyle advise, watchful waiting, indwelling catheter, and intermittent catheterization are discussed. Transurethral microwave thermotherapy (TUMT), Transurethral needle ablation (TUNA) and Prostate stent are discussed in the next chapter (Chapter 10: Surgery.)

Table. Level of Evidence and Grade of Recommendations for Conservative therapies

<table>
<thead>
<tr>
<th>Modification</th>
<th>Level</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle advises prior to or concurrent with treatment can provide the opportunity for treatment of BPH and LUTS.</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>Men with mild symptoms are suitable for watchful waiting.</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>The use of chronic indwelling catheter is necessary for patients who have refractory retention and high surgical risk.</td>
<td>5</td>
<td>C1</td>
</tr>
<tr>
<td>Intermittent catheterization is associated with less UTI compared to indwelling catheter and early recovery of bladder function following surgery for urinary retention.</td>
<td>2</td>
<td>B</td>
</tr>
</tbody>
</table>

10.2.1 Lifestyle advises/modifications

Lifestyle factors play some part in the pathogenesis of BPH and LUTS. Lifestyle factors associated with increased risks of BPH and LUTS include obesity, diabetes, and meat and fat consumption [1]. In contrast, factors associated with decreased risks include exercise, and vegetable consumption. Modification of these factors can provide the opportunity for treatment of BPH and LUTS. This approach has noninvasiveness and low financial burden. Lifestyle advises and recommended modifications for BPH and LUTS should probably include the following [2, 3].

Modifications of fluid intake; Reduction of fluid intake at specific times is necessary for patients with storage symptoms, and the recommended total daily
fluid intake for an average man with LUTS should be 1500–2000mL. For nocturia, evening fluid restriction 2 hours prior to sleeping is appropriate. Avoidance or moderation of certain dietary factors which may have a diuretic and irritant effect such as caffeine, alcohol, and spices. Use of relaxed voiding, double-voiding techniques and urethral milking to prevent post micturition dribble. Distraction techniques, such as penile squeeze, breathing exercises, perineal pressure and mental ‘tricks’ to take the mind off the bladder and toilet, to help control irritative symptoms. Bladder re-training, by which men are encouraged to ‘hold on’ when they have sensory urgency to increase their bladder capacity (to around 400mL) and the time between voids. Optimizing the time of administration medication or substituting drugs for others that have fewer urinary effects. Providing necessary assistance when there is impairment of dexterity, mobility or mental state. Avoid constipation.

Education and reassurance

(Level of evidence 2, grade recommendation B)

10.2.2 Watchful waiting

There is some evidence to support the efficacy of watchful waiting [4, 5]. Men who have not bothersome or mild uncomplicated LUTS are suitable for watchful waiting which is not medical or surgical treatment but include education, reassurance, periodic monitoring, and lifestyle advice. Progression of symptoms is rare [6] and delayed treatment intervention is still effective in those patients. A large study comparing watchful waiting and transurethral resection of the prostate in men with moderate symptoms showed that those who had undergone surgery had improved bladder function over the watchful waiting group. Thirty six percent of patients crossed over to surgery in 5 years, leaving 64% doing well in the watchful waiting group [7]. For adequate patient selection, physicians have to consider clinical findings because prostate-specific antigen, obstructive symptom score, and transitional zone volume were identified as important risk factors of clinical progression [8]. Watchful waiting patients usually are recommended reexamination every 12 months.

(Level of evidence 2, Grade of recommendation B)
10.2.3 Complementary/alternative medicine (CAM)
Most complementary and alternative medicines for BPH are extracts of the roots, the seeds, the bark, or the fruits of the various plants. Among these, the most commonly used and investigated product is an extract of the berry of the saw palmetto (Serenoa repens). However, recent clinical trials have questioned their efficacy and increasing doses of a saw palmetto extract did not improve LUTS more than placebo [9, 10]. Other products include extracts of the African plum tree (Pygeum africanum), stinging nettle (Urtica dioica), pumpkin seed (Curcubita pepo), South African star grass (Hypoxis rooperi) and rye pollen (Secale cereal). Complementary and alternative medicines other than saw palmetto and Urtica dioica do not have evidence to support efficacy and safety. (Level of evidence 2, grade of recommendation D)

10.2.4 Urethral indwelling catheter/Suprapubic catheter
The use of chronic indwelling catheter is necessary for patients who have refractory retention and high surgical risk. However, it is associated with several complications and significant impairment of quality of life. Urethral indwelling catheter is technically easier, less morbid compared to suprapubic catheterization, but its disadvantages are higher risk of injury to the urethra and bladder neck [11]. Selection of management for patients with chronic indwelling catheter should depend on the long term comfort for the patient and a physician mind-set.
Patients who are on the waiting for definitive surgery after acute urinary retention (AUR) need to indwell catheter too. In prospective cross-sectional survey, the initial management of AUR consisted of urethral indwelling catheter and suprapubic catheter in 83% and 17% respectively [12]. (Level of evidence 5, grade recommendation C1)

10.2.5 Intermittent catheterization
Intermittent catheterization is an alternative to an indwelling catheter in patients who are capable of catheterizing themselves. It is associated with less urinary tract infection compared to indwelling catheter [13]. There is evidence for early recovery of bladder function following surgery for urinary retention [14]. It can have a good effect of quality of life, especially sexual life. However it is not appropriate in advanced old aged patients who may lack the
mobility, visual acuity, or cognitive ability to manage self-catheterization. In addition, patients with severe prostate enlargement have difficulty in urethral catheterization if they do not have special skills or equipments.

(Level of evidence 2, grade of recommendation B)

References


11. Recommended grade for treatment: Surgery

Wachira Kochakarn, M.D., Ph.D.

Absolute indications for surgery in patients with BPH/LUTS/BPE/BOO are refractory urinary retention, recurrent urinary tract infection from BOO, refractory hematuria due to BPH, renal insufficiency from chronic BOO, vesical calculi or diverticulum. According to aging not only in Western countries but Asian countries, such BPH patients are often at high risk for surgical interventions. According to Treatment Algorithm (Chapter 1. Algorithm, d. Treatment Algorithm of Bothersome Male LUTS Refractory to Medical/Conservative Treatment or Absolute Surgical Indications for Urologist), American Society of Anesthesiologists Operative Risk Assessment of Physical Status Class, treatment recommendation are summarized in the following Table.

Table. Treatment recommendation according to operative risk assessment, and prostate volume.

<table>
<thead>
<tr>
<th>Operative Risk Assessment</th>
<th>Prostate Volume</th>
<th>Remark</th>
<th>Recommended treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA PS class IV</td>
<td></td>
<td>Conservative</td>
<td>CIC, Indwelling Catheterization etc.</td>
</tr>
<tr>
<td>ASA PS class III, on anti-coagulation drug</td>
<td></td>
<td>Laser</td>
<td>PVP, Thulium laser, HoLAP, HoLEP</td>
</tr>
<tr>
<td>ASA PS class I or class II</td>
<td>&gt;80 ml</td>
<td>Classical/Laser</td>
<td>TURP, TUEB, PVP, Thulium laser, HoLEP</td>
</tr>
<tr>
<td>ASA PS class I or class II</td>
<td>30-80 ml</td>
<td>Classical/Laser/MIST</td>
<td>TURP, TUEB, PVP, Thulium laser, HoLEP, TUMT, TUNA</td>
</tr>
<tr>
<td>ASA PS class I or class II</td>
<td>&lt;30 ml</td>
<td>Classical/MIST</td>
<td>TURP, TUIP</td>
</tr>
</tbody>
</table>

ASA: American Society of Anesthesia, PS; Performance Status, MIST; Minimal invasive therapy
11.1 Transurethral resection of prostate (TURP)

TURP is the gold standard of surgical treatment of symptomatic BPH. An indication that is accepted for TURP is for moderate to severe symptoms and for those who fail to respond to medical treatment or don’t accept to medical therapy. Many changes have undergone to improve outcome of TURP and incur less complications such as optic quality, light sources, surgical and anesthetic technique [1].

The current indications for TURP are moderate to severe bothersome symptoms, recurrent urinary retention, bladder stones, obstructive renal failure and hematuria due to prostate gland enlargement. Due to improvement of instrument and technique including continuous sheath, TURP can be performed in bigger gland than prior reported. In fact, prostate gland of 120 g can be done with a minimal complication [2].

Complications of TURP [3] are TURP syndrome (1.4%), bleeding need for blood transfusion (<20%), urethral stricture (10%). Mortality is less than 1 %. Bipolar TURP is believed for fewer complications, especially TURP syndrome and urethral stricture but there are data giving support of less complications as well as a cost-analysis [4-7].

(Level 1 Evidence, Grade A Recommendation)

11.2 Transurethral incision of prostate (TUIP)

TUIP is indicated for men who have moderate to severe symptoms but reveal small prostate gland. The accepted indication for TUIP is less than 30 g.

Long-term symptomatic improvement in TUIP is similar to TURP but with less incidence of retrograde ejaculation [8].

(Level 2 Evidence, Grade B Recommendation)

11.3 KTP (greenlight)

Laser vaporization is associated with a low risk of hemorrhage and can be performed safely even on large prostates [9-11]. Photoselective vaporization prostatectomy (PVP) or greenlight laser is another optional treatment in men with symptomatic BPH who might have bleeding tendency. RCT comparing to TURP shows comparable shortterm outcome but higher in reoperation in PVP [11]. There is significant blood loss and shorten catheterization in PVP group when compared to standard TURP. High voltage PVP (120 watts) is
recommended for use in a very large gland due to less time consumed in using 80 watts PVP [12].
There is sufficient evidence for the effectiveness and sustainability of laser vaporization of the prostate, although tissue sampling is impossible, unlike TURP.

(Level 2 Evidence, Grade B Recommendation)

11.4 HoLEP
Holmium laser enucleation (HoLEP) is recommended for large prostate gland of more than 50 g with bleeding tendency, including patients who take anticoagulant [13-16]. RCT comparing HoLEP to TURP has demonstrated impressive outcomes, especially in term of Qmax at 12 months after treatment. But HoLEP has overall complication less than TURP (8.1% v.s.16.2%) [13].

(Level 1 Evidence, Grade B Recommendation)

11.5 Open prostatectomy
Open prostatectomy remains indicated as one of the optional treatments of BPH, especially too large for TURP for fear of incomplete resection, massive bleeding and dilutional hyponatremia [17]. Open prostatectomy is also indicated for concomitant pathologies needing a surgical approach such as vesical stones and diverticula.

(Level 3 Evidence, Grade C1 Recommendation)

Special situations
We categorize patients into 2 groups; patients, who can’t stop anti-coagulation and who are not fit for surgery/general anesthesia.

1) Patient, who can’t stop anti-coagulation
   a. KTP (greenlight)
      (Level 2 Evidence, Grade B Recommendation)
   b. HoLEP
      (Level 1 Evidence, Grade B Recommendation)
2) Patient, who are not fit for surgery/general anesthesia
a. Transurethral microwave thermotherapy (TUMT) and Transurethral needle ablation (TUNA)

Transurethral microwave thermotherapy (TUMT) and transurethral needle ablation (TUNA) are indicated in high risk patients especially having bleeding tendency and volume overload [18]. This kind of treatment can be performed without anesthesia. Due to less improvement of symptoms [18] when compared to standard treatment and introduction of any kind of laser therapy, TUMT is performed less frequent during the last decade. TUNA is considered contraindicated in prior radiation to pelvic organ due to higher risk of rectal fistula [19].

(Level 1 Evidence, Grade C Recommendation)

b. Prostate stent

Prostate stents have been indicated in elderly men with significant comorbidities which are therefore unfit for surgery [20,21]. Two types of stent are introduced as temporary and permanent stent.

(Level 3 Evidence, Grade D Recommendation)

Reference


### 12. Abbreviations used in the text

This list is not comprehensive for the most common abbreviations.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>American Society of Anesthesia</td>
</tr>
<tr>
<td>AVP</td>
<td>Arginine vasopressin</td>
</tr>
<tr>
<td>AUA</td>
<td>American Urological Association</td>
</tr>
<tr>
<td>BOO(I)</td>
<td>Bladder outlet obstruction (index)</td>
</tr>
<tr>
<td>BPE</td>
<td>Benign prostatic enlargement</td>
</tr>
<tr>
<td>BPH</td>
<td>Benign prostatic hyperplasia</td>
</tr>
<tr>
<td>BPO</td>
<td>Benign prostatic obstruction</td>
</tr>
<tr>
<td>cGMP</td>
<td>Cyclic guanosine monophosphate</td>
</tr>
<tr>
<td>CIC</td>
<td>Clean intermittent catheterization</td>
</tr>
<tr>
<td>CombAT</td>
<td>Combination of avodart® and tamsulosin</td>
</tr>
<tr>
<td>DHT</td>
<td>Dihydrotestosterone</td>
</tr>
<tr>
<td>DRE</td>
<td>Digital rectal examination</td>
</tr>
<tr>
<td>EAU</td>
<td>European Association of Urology</td>
</tr>
<tr>
<td>EBM</td>
<td>Evidence-based medicine</td>
</tr>
<tr>
<td>ED</td>
<td>Erectile dysfunction</td>
</tr>
<tr>
<td>EjD</td>
<td>Ejaculation dysfunction</td>
</tr>
<tr>
<td>eNOS</td>
<td>Endothelial nitric oxide synthase</td>
</tr>
<tr>
<td>ER</td>
<td>Extended release</td>
</tr>
<tr>
<td>FVC</td>
<td>Frequency volume chart</td>
</tr>
<tr>
<td>GITS</td>
<td>Gastrointestinal therapeutic system</td>
</tr>
<tr>
<td>GP</td>
<td>General practitioner</td>
</tr>
<tr>
<td>HoLAP</td>
<td>Holmium laser ablation of the prostate</td>
</tr>
<tr>
<td>HoLEP</td>
<td>Holmium laser enucleation of the prostate</td>
</tr>
<tr>
<td>IFIS</td>
<td>Intra-operative floppy iris syndrome</td>
</tr>
<tr>
<td>IPP</td>
<td>Intravesical protrusion of prostate</td>
</tr>
<tr>
<td>IPSS</td>
<td>International prostate symptom score</td>
</tr>
<tr>
<td>IR</td>
<td>Immediate release</td>
</tr>
<tr>
<td>KTP</td>
<td>Potassium titanyl phosphate</td>
</tr>
<tr>
<td>LUTS</td>
<td>Lower urinary tract symptoms</td>
</tr>
<tr>
<td>MIST</td>
<td>Minimal invasive therapy</td>
</tr>
<tr>
<td>MR</td>
<td>Modified release</td>
</tr>
<tr>
<td>MTOPS</td>
<td>Medical therapy of prostatic symptoms</td>
</tr>
<tr>
<td>NAION</td>
<td>Non-arteritic anterior ischemic optic neuropathy</td>
</tr>
</tbody>
</table>
NO  Nitric oxide
NOS  NO synthases
nNOS  Neuronal nitric oxide synthase
n.s.  Not significant
OAB  Overactive bladder
OCAS  Oral controlled absorption system
PA  Prostatic adenoma
PDE  Phosphodiesterase
PFS  Pressure-flow study
PS  Performance Status
PSA  Prostate specific antigen
PV  Prostate volume
PVP  Photoselective vaporization of the prostate
PVR  Post-void residual urine
Qmax  Maximum urinary flow rate during free uroflowmetry
QoL  Quality of life
RR  Relative risk
SHBG  Sexual hormone binding globulin
SR  Sustained release
tmax  Time to maximum plasma concentration
t½  Elimination half-life
TUEB  Transurethral enucleation of prostate using bipolar electrode
TUERP  Transurethral enucleation and resection of the prostate
  (either using bipolar or monopolar electrode)
TUIP  Transurethral incision of the prostate
TUMT  Transurethral microwave therapy
TUNA  Transurethral needle ablation
TURP  Transurethral resection of the prostate
TUVP  Transurethral vaporization of the prostate
UTI  Urinary tract infection
WW  Watchful waiting