Benign Prostatic Hyperplasia: Current Medical Treatments

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BPH: Definitions and Terminology

- Benign prostatic hyperplasia is defined as a disease process characterized by stromal and epithelial cell hyperplasia beginning in the periurethral zone of the prostate.
BPH: Definitions and terminology

- The chief complaint of a patient with BPH is usually bothersome LUTS typified by urinary frequency, urgency, nocturia, decreased and intermittent force of stream, and the sensation of incomplete bladder emptying.

- “LUTS suggestive of BPH” now used in place of older term “prostatism”
Figure 1 The prostate is composed of three distinct zones: the peripheral zone (PZ); the transitional zone (TZ); and the central zone (CZ) (anteroposterior view). Prostate cancer most commonly originates in the PZ; in contrast, BPH almost exclusively affects the TZ and periurethral tissues.

Figure 2 The three zones of the prostate (sagittal view)
BPH: Demographics

• The prevalence of histopathologic BPH is age dependent, with initial development usually after 40 years of age.
• By 60 years of age, its prevalence is greater than 50% and by age 85 is as high as 90%.
• The prevalence of bothersome symptoms also increases with age.
BPH: Natural history

• Symptoms worsen in 55% of patients
• Remain stable in 30%
• Improve in 15%
• Clinical progression includes worsening of bother, decrease in quality of life, need for surgery, and urinary retention
• Factors associated with risk of progression include age, symptom severity, prostate volume, and PSA
BPH: Natural History

- Prostate size increases at a rate of 0.6ml/yr for all men.
- Men with prostate volume >40 ml are 3 times as likely to have elevated symptoms, and twice as likely to experience interference with normal daily activities.
- Men with prostate size >30 ml have a three fold risk for acute urinary retention.
BPH: Natural History

• Risk factors for progression
  – change in size and force of stream
  – sensation of incomplete voiding
  – enlarged prostate on DRE.
  – risk of AUR/surgery increases with the number of risk factors
    • 1=9%
    • 2=16%
    • 3=37%
BPH: Pathophysiology

• The growth and development of the prostate is under the influence of the male hormone testosterone and its more active metabolite, dihydrotestosterone (DHT).
• The enzyme responsible for the conversion of testosterone to DHT is 5 alpha reductase.
• The development of histological BPH requires aging and androgens
BPH: Pathophysiology

- BPH requires DHT stimulation of androgen receptors; this results in the transcription and translation of growth factors, such as epidermal growth factor (EGF).
- This in turn promotes the stromal and epithelial hyperplasia characteristic of BPH.
Figure 1.2 (a) In the normal prostate, cell formation is balanced by programmed cell death (apoptosis). (b) BPH develops when growth factors such as epidermal growth factor (EGF) promote excessive cell division or when lack of transforming growth factor β (TGF β) reduces the rate of cell death.
BPH: Initial Evaluation
Recommended

• A medical history should be taken to identify other causes of voiding dysfunction or comorbidities that may complicate treatment.

• A physical examination, including both a digital rectal examination (DRE) and a focused neurologic examination, should be performed.

• A urinalysis should be performed by dipstick testing or microscopic examination of the sediment to screen for hematuria and UTI.
Figure 1.1. Benign prostatic hyperplasia diagnosis and treatment

- Initial Evaluation
  - History
  - DRE & Focused PE
  - Urinalysis
  - PSA in Select Patients

- AUA/IPSS Symptom Index Assessment of Patient Bothers
  - Mild Symptoms (AUA/IPSS ≤ 7) or No Bothersome Symptoms
  - Moderate/Severe Symptoms (AUA/IPSS ≥ 8)
    - Optional Diagnostic Tests
      - Uroflow
      - PVR
    - Discussion of Treatment Options

- Presence of Refractory Retention or Any of the following clearly related to BPH
  - Persistent Gross Hematuria
  - Bladder Stones
  - Recurrent UTIs
  - Renal Insufficiency

- Patient Chooses Noninvasive Therapy
  - Watchful Waiting
  - Medical Therapy

- Patient Chooses Invasive Therapy
  - Optional Diagnostic Tests
    - Pressure Flow
    - Urethrocytoscopy
    - Prostate Ultrasound
  - Minimally Invasive Therapies
  - Surgery

- Surgery

*In patients with clinically significant prostatic bleeding, a course of a 5 alpha-reductase inhibitor may be used. If bleeding persists, tissue ablative surgery is indicated.

†Patients with at least a 10-year life expectancy for whom knowledge of the presence of prostate cancer would change management or patients for whom the PSA measurement may change the management of voiding symptoms.

‡After exhausting other therapeutic options as discussed in detail in the text.

§Some diagnostic tests are used in predicting response to therapy. Pressure flow studies are most useful in men prior to surgery.

DRE, digital rectal exam; IPSS, International Prostate Symptom Score; PE, physical exam; PSA, prostate-specific antigen; UTI, urinary tract infection.
BPH: Initial evaluation and PSA

- Approximately 25% of men with BPH have a serum PSA > 4 ng/ml.
- Because of the overlap between serum PSA values in men with BPH and those with clinically localized prostate cancer, PSA velocity, free/total PSA ratio, complexed PSA and PSA density measurements may help improve diagnostic specificity.
- Don’t forget the DRE!
BPH: Optional Diagnostic Tests

- Following the initial evaluation of the patient, urinary flow rate recording and the measurement of postvoid residual urine (PVR) may be appropriate.
- These tests usually are not necessary prior to the institution of watchful waiting or medical therapy.
- However, they may be helpful in patients with a complex medical history and in those desiring invasive therapy.
- Cystoscopy is used in hematuria, but can also be useful to assess anatomy or look for other pathological conditions.
BPH: Symptom Assessment; Recommended

- The AUA Symptom Index should be used as the scoring instrument in the initial assessment of each patient presenting with BPH.
- Other validated assessment instruments are optional (ie. Danish Prostate Symptom Score, International Continence Society)
BPH: Initial Management

- Patients with mild symptoms of BPH (AUA Symptom Score $\leq 7$) and patients with moderate or severe symptoms (AUA Symptom Score $> 8$) who are not bothered by their symptoms, should be managed using a strategy of watchful waiting.
BPH: Moderate to Severe Symptoms

- Treatment options for patients with bothersome moderate to severe symptoms of BPH (AUA Symptom Score >8) include watchful waiting and medical, minimally invasive or surgical therapies.

- Information on the benefits and risks of BPH treatment options (including watchful waiting) should be explained to patients with moderate to severe symptoms who are bothered enough to consider therapy.
Table 1.1. Treatment options for patients with moderate to severe symptoms of benign prostatic hyperplasia

<table>
<thead>
<tr>
<th>Watchful Waiting</th>
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<tbody>
<tr>
<td><strong>Medical Therapies</strong></td>
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<tr>
<td>Alpha-adrenergic blockers</td>
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<tr>
<td>Alfuzosin</td>
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<tr>
<td>Doxazosin</td>
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<tr>
<td>Tamsulosin</td>
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<tr>
<td>Terazosin</td>
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<tr>
<td>5 alpha-reductase inhibitors</td>
</tr>
<tr>
<td>Dutasteride*</td>
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<tr>
<td>Finasteride</td>
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<tr>
<td>Combination therapy (alpha blocker and 5 alpha-reductase inhibitor)†</td>
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<tr>
<th>Minimally Invasive Therapies</th>
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<tr>
<td>Transurethral microwave heat treatments</td>
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<tr>
<td>CoreTherm™</td>
</tr>
<tr>
<td>Prostatron® (various versions)</td>
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<tr>
<td>Targis®</td>
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<tr>
<td>TherMatrix™</td>
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<tr>
<td>Transurethral needle ablation</td>
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<tr>
<td>UroLume® stent†</td>
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<th>Surgical Therapies</th>
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<tr>
<td>Transurethral resection of the prostate</td>
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<td>Transurethral electrovaporization</td>
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<tr>
<td>Transurethral incision of the prostate</td>
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<tr>
<td>Transurethral holmium laser resection/enucleation</td>
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<tr>
<td>Transurethral laser vaporization</td>
</tr>
<tr>
<td>Transurethral laser coagulation (e.g., visual laser ablation)</td>
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<tr>
<td>Open prostatectomy</td>
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*Recommendations based on randomized, controlled trials not included in the outcomes tables
†The Panel assumes that the combination of any effective alpha blocker and 5 alpha-reductase inhibitor probably produces a comparable benefit. However, the best-tested combination is doxazosin and finasteride. The safety of specific combinations other than finasteride plus doxazosin, terazosin, and alfuzosin has not been assessed.
‡Recommended for a subset of patients, see text
BPH: Additional Studies

• Filling cystometography (CMG) and imaging of the upper urinary tract by ultrasound or IVP are not recommended in the evaluation of the typical patient with symptoms of BPH, unless the patient has hematuria, UTI, renal insufficiency, or a history of urolithiasis or urinary tract surgery.
BPH: Alpha Blocker Therapy

- Alfuzosin, doxazosin, tamsulosin, and terazosin are appropriate treatment options for patients with LUTS secondary to BPH.
- work on the 3 subtypes of alpha 1 receptors, a1a is most concentrated within the prostate
- The primary adverse events reported with alpha blocker therapy are orthostatic hypotension, dizziness, tiredness, ejaculatory problems, and nasal congestion.
- 4-6 point improvement in auass.
BPH: 5 alpha reductase inhibitor therapy

- 5 alpha reductase inhibitors finasteride and dutasteride are appropriate for patients with LUTS associated with demonstrable prostatic enlargement.
- Patients with symptomatic prostatic enlargement but without signs of bother may be offered a 5-alpha reductase inhibitor to prevent progression of the disease (discuss risks/benefits).
- 3 point improvement in auass long term.
- Not appropriate for men with LUTS without prostatic enlargement.
- Adverse events are primarily sexually related and reversible.
BPH: Combination Therapy

- The combination of an alpha blocker and a 5-alpha reductase inhibitor is an appropriate and effective treatment for patients with LUTS with demonstrable prostatic enlargement.
- Main advantage is reduction in overall risk of progression leading to retention or surgery.
Benign Prostatic Hyperplasia: Current Surgical and Minimally Invasive Treatments

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BPH: Minimally Invasive Therapies

• Thermal based therapies:
  – Transurethral microwave heat treatment
  – Radio Frequency waves (TUNA)
    • 10-13 unit AUASS reduction
    • 3 to 5 ml/sec improvement in flow
  – High Intensity Ultrasound (HIFU)
  – Interstitial Laser (Indigo)
  – All achieve temperatures greater than 45 degrees C. to produce tissue coagulation
  – Lower cost and morbidity than TURP
  – UroLift
BPH: Surgery

- The patient may appropriately select surgical treatment as his initial treatment if he has bothersome symptoms. Patients who have developed complications of BPH are best treated surgically.
- The choices of surgical approach are technical decisions based on the patient’s prostate size, the individual surgeons judgment, and the patient’s comorbidities.
BPH: Surgery

- TURP
- TUVP
- TUIP
- Laser Prostatectomy (contact)
- VLAP, Greenlight laser prostatectomy
- Open Prostatectomy
BPH: Surgery

• Surgery is recommended for patients with refractory retention who have failed at least one attempt at catheter removal. In patients who are not surgical candidates, treatment with intermittent catheterization, or an indwelling catheter is recommended.

• Concomitant administration of an alpha blocker is an option prior to attempted catheter removal in patients with urinary retention.
BPH: Surgery

• Surgery is recommended for patients who have renal insufficiency clearly due to BPH and in those patients with recurrent UTI’s, recurrent gross hematuria, or bladder stones clearly due to BPH and refractory to other therapies.
BPH: Emerging Therapies

- Phytotherapeutic Agents
- Absolute Ethanol Injection
- High intensity focused ultrasound
- UroLift
- Trans-urethral heat based therapies
  - Interstitial Laser coagulation
  - Water induced thermotherapy
  - Plasmakinetic tissue management
BPH: Conclusion

• Guidelines enable practitioners to enhance efficiency and efficacy in the evaluation and treatment of BPH
• There are many options for the patient and physician to tailor treatment to the individual’s needs.
• Emerging technologies should and will be addressed in future guidelines.