BPH/ LUTS: Medical Treatment

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Content

- Epidemiology
- Diagnostics and Classification
- Medical Treatment
- Case Studies
Case 1

- 64 year old male patient
- Seeking treatment with complaints of LUTS
- TRUS 48 ml, PVR: 64 ml, Qmax 10.4 ml/s, IPSS: 17/4

What would you recommend?

1. Watchful waiting/LS-Advise 4. 5-α-Reductase-Inhibitor
2. Phytotherapy 5. Combination-Therapy (3.+4.)
3. α-Blocker 6. Surgery
Content

• Epidemiology

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• Medical Treatment

• Case Studies
What is LUTS?
Epidemiology in Europe

Up to 24 million men in the EU\(^1,2\) >50 years old are affected by moderate-to-severe LUTS due to BPH

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Epidemiology in Germany

12 Mio.
Men > 50 Years
(Germany)

5 Mio.
LUTS (IPSS >7)

3.2 Mio.
BPE (>25 ml)

2.1 Mio.
BOO ($Q_{\text{max}} <10 \text{ ml/s}$)

+ relevant bother

60% moderate symptoms

90% severe symptoms

„Herner LUTS-Study“

How does bother look like?
BPH is a progressive disease

4-year cumulative incidence of clinical progression* = 17%

*Clinical progression is defined as an increase above baseline of ≥4 points in the AUA symptom score, acute urinary retention, urinary incontinence, renal insufficiency, or recurrent urinary tract infection.
Disease Progression

- Data from untreated patient populations:
  - Epidemiologic studies (Olmsted County Study/ Tirol LUTS-Study\(^1\))
  - Placebo-Arms of prosp.-rand. trials (MTOPS\(^2\))

<table>
<thead>
<tr>
<th>Progression</th>
<th>Likelihood *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall progression</td>
<td>17(^2) (30(^1))</td>
</tr>
<tr>
<td>Symptomatic progression:</td>
<td>79(^2)</td>
</tr>
<tr>
<td>≥4 IPSS-Punkten</td>
<td></td>
</tr>
<tr>
<td>Clinical progression:</td>
<td>9(^2)</td>
</tr>
<tr>
<td>Rec. UTI, Incontinence, Hydronephrosis …</td>
<td></td>
</tr>
<tr>
<td>AUR</td>
<td>12(^2)</td>
</tr>
</tbody>
</table>

* Reference-Intervall 5 years

\(^1\) Jimenez-Cruz et al. (2003) Eur Urol, Suppl 2: 6-12
## Disease Progression

### Risk Factors (MTOPS)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>&gt; 62 years</td>
</tr>
<tr>
<td><strong>Volume</strong></td>
<td>&gt; 31 ml</td>
</tr>
<tr>
<td><strong>PSA</strong></td>
<td>&gt; 1.6 µg/l</td>
</tr>
<tr>
<td><strong>Q\textsubscript{max}</strong></td>
<td>&lt; 10.6 ml/s</td>
</tr>
<tr>
<td><strong>IPSS</strong></td>
<td>&gt; 17</td>
</tr>
<tr>
<td><strong>PVR</strong></td>
<td>&gt; 39 ml</td>
</tr>
</tbody>
</table>

## AUR- risk factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference</th>
<th>Target variable</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [Years]</td>
<td>40-49</td>
<td>70-79</td>
<td>7.9</td>
</tr>
<tr>
<td>$Q_{\text{max}}$ [ml/s]</td>
<td>&gt;12</td>
<td>≤12</td>
<td>3.9</td>
</tr>
<tr>
<td>IPSS</td>
<td>0-7</td>
<td>8-35</td>
<td>3.2</td>
</tr>
<tr>
<td>Prostate volume [ml]</td>
<td>≤30</td>
<td>&gt;30</td>
<td>3.0</td>
</tr>
<tr>
<td>PSA [ng/ml]</td>
<td>≤1.4</td>
<td>&gt;1.4</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Content

- Epidemiology
- Diagnostics and Classification
- Medical Treatment
- Case Studies
Diagnostic Work-up
Male LUTS - Assessment

Male LUTS

- Questionnaire with QoL (e.g. IPSS)
  - History
    - Physical Examination
  - Urinalysis (stix, sediment)
  - Blood Analysis (Na⁺, serum-creatine, PSA)
  - Ultrasound (bladder, prostate, kidneys)
  - Uroflowmetry
  - Bladder Diary (in cases of nocturia or polyuria)
  - Benign Conditions of Bladder and/or Prostate with baseline values

- Additional tests necessary according to abnormalities found during initial assessment, see other EAU Guidelines

In patients with negative findings after additional evaluation

- Treatment Male LUTS

Neurological diseases – neurogenic bladder dysfunction, drug-induced LUTS, heart diseases with nocturnal polyuria, penile diseases (e.g. phimosis, meatal stenosis, lichen sclerosus, penile cancer), palpable prostate carcinoma ...

Urinary tract infection, haematuria, diabetes mellitus ...

Deterioration of kidney function (e.g. due to distal ureter stone or transitional cell carcinoma), prostatitis ...

Benign prostatic enlargement (BPE), prostate tumor/cyst, pelvic tumour, post-void residual urine, urinary retention, bladder stone, bladder tumour, bladder diverticulum, foreign body in bladder, distal ureter stone, hydronephrosis ...

Urethral stricture, dysfunctional voiding ...

Nocturnal polyuria, polycipsia-polyuria, diabetes insipidus ...

### International Prostate Symptom Score

- Validated Score Sheath
- Symptoms over past 4 weeks

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete Emptying</td>
<td>5</td>
</tr>
<tr>
<td>Frequency</td>
<td>5</td>
</tr>
<tr>
<td>Intermittency</td>
<td>5</td>
</tr>
<tr>
<td>Urgency</td>
<td>5</td>
</tr>
<tr>
<td>Weak Stream</td>
<td>5</td>
</tr>
<tr>
<td>Straining</td>
<td>5</td>
</tr>
<tr>
<td>Nocturia</td>
<td>5</td>
</tr>
</tbody>
</table>

**Your Total I-PSS Score**

If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?
### Symptom Classification

<table>
<thead>
<tr>
<th>Evaluated Symptoms</th>
<th>IPSS-Score</th>
<th>Classification</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Incomplete emptying</td>
<td>0–7</td>
<td>Mild</td>
<td>Little burden, appropriate Qmax, low PVR</td>
</tr>
<tr>
<td>• Frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Intermittency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Urgency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Weak stream</td>
<td>8–19</td>
<td>Moderate</td>
<td>Troublesome symptoms, no complications</td>
</tr>
<tr>
<td>• Straining</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Nocturia</td>
<td>≥ 20</td>
<td>Severe</td>
<td>Complications due to obstruction</td>
</tr>
<tr>
<td>• Quality of Life (due to BPH)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Urodyamics

Indications:

• Patient cannot void > 150 ml
• Qmax > 15 ml/s
• Age < 50 or > 80 years
• PVR > 300 ml, although „sufficient“ voiding
• Suspected: neurogenic lesion
• Post unsuccessful invasive treatment
Content

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Aim of treatment

Patient:
- Reduce symptoms

Doctor:
- Reduce symptoms
- Reduce risk of progression
- Reduce risk of complications
Medical (conservative) Treatment

Options:

• Watchful Waiting – behavioural treatment
• Muscarinic receptor antagonists
• Vasopressin analogue – Desmopressin
• PDE-5 Inhibitors
• (Plant extracts)
• α-Blockers
• 5-α-Reductase-Inhibitors
• Combination therapy
Watchful Waiting + Behavioural T.

- Option for men with mild symptoms
- ~ 65% of patients will still continue WW within 5 years
- Life style advise important factor (sign. higher IPSS reduction):
  - Reduction of fluid intake
  - Moderation of alcohol and caffeine
  - Double voiding
  - Urethral stripping

Men with mild symptoms are suitable for watchful waiting.
Men with lower urinary tract symptoms should be offered lifestyle advice prior to or concurrent with treatment.

Muscarinic receptor antagonists:

<table>
<thead>
<tr>
<th>LE</th>
<th>GR</th>
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<tbody>
<tr>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>4</td>
<td>C</td>
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</table>

Muscarinic receptor antagonists might be considered in men with moderate to severe lower urinary tract symptoms who have predominantly bladder storage symptoms. Caution is advised in men with bladder outlet obstruction.

Vasopressin analogue – Desmopressin

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Desmopressin can be used for the treatment of nocturia secondary to nocturnal polyuria.

PDE-5 Inhibitors

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PDE5 inhibitors reduce moderate to severe male lower urinary tract symptoms. PDE5 inhibitors are currently restricted to men with erectile dysfunction, pulmonary arterial hypertension, or to those who have lower urinary tract symptoms and participate in clinical trials.
α-Blockers

- 5 α-blockers are currently in use:
  - Alfuzosin (2-3 x/d), Doxazosin, Tamsulosin, Terazosin, Silodosin
  - Reduce IPSS by 35-40%
  - Increase Qmax by 20-25%
  - Onset within hours/days
  - No effect on prostate volume
  - No effect on risk of progression/AUR

α-blockers relax the smooth muscle receptors in the bladder neck and within the prostate

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</table>
5-α-Reductase-Inhibitor

- Two drugs available:
  - Finasteride (Inhibiting 5-AR Type 2)
  - Dutasteride (Inhibiting 5 –AR Type 1 + 2)

- Inhibition causes:
  - Reduction in DHT - 70–95%
  - Apoptosis
  - Reduction of P-Volume (~ 18–28%)
  - Reduction of PSA (~ 50%)

5α-reductase inhibitors should be offered to men who have moderate-to-severe lower urinary tract symptoms and enlarged prostates (> 40 mL) or elevated prostate specific antigen concentrations (> 1.4 – 1.6 μg/L). 5α-reductase inhibitors can prevent disease progression with regard to acute urinary retention and need for surgery.

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<td>A</td>
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</table>

5ARIs inhibit the AR axis inhibiting the growth of the cells within the prostate
Combination Therapy

1. α-Blocker + 5-α-Reductase-Inhibitor

1. α-Blocker + Muscarinic Receptor Antagonist

<table>
<thead>
<tr>
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<th>GR</th>
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<tbody>
<tr>
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<td>B</td>
</tr>
</tbody>
</table>

Combination treatment with α₁-blocker and muscarinic receptor antagonist might be 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.

<table>
<thead>
<tr>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>
α-Blocker + 5-α-Reductase-Inhibitor

- Principle: Combine different effects for synergistic efficacy.
- Fast onset of α-Blocker class
- Risk-reduction of 5-α-Reductase-Inhibitor class

Goal of combination therapy:
- Reduce IPSS
- Reduce risk of disease progression
- Reduce risk of AUR and BPH-related surgery
CombAT: IPSS

Baseline Study month Adjusted mean change from baseline in IPSS

Tamsulosin (n=1582) Dutasteride (n=1592) Combination (n=1575)

P <0.001 combination versus tamsulosin
P <0.001 combination versus dutasteride

Adjusted mean change from baseline in IPSS

CombAT: Qmax

Adjusted mean change from baseline in Qmax (ml/s)

Study month

- Combination (n=1495)
- Dutasteride (n=1505)
- Tamsulosin (n=1523)
CombAT: Vol.- Reduction (4 y.)

Combined mean percentage change

Total prostate volume

-27.3%  -28.0%  -17.9%  -26.5%

Transition zone volume†

4.6%* 18.2%*

For combination versus tamsulosin at Year 4:
Relative risk reduction = 65.8%
Absolute risk reduction = 7.7%
NNT: 13 patients
Dutasterid: cont. PSA decrease

Men who had not reached PSA nadir (%)

Month

87% 70% 49% 44% 32% 19% 3% 0

6 12 18 24 30 36 42 48
Dutasteride: cont. PSA decrease

REDUCE: mean PSA change over time in men with or without prostate cancer

- Placebo
- Cancer (n=858)
- No cancer (n=2566)

- Dutasteride:
- Cancer (n=659)
- No cancer (n=2646)
5ARI therapy - When to start?

<table>
<thead>
<tr>
<th>Event</th>
<th>Early (20.0%)</th>
<th>Late (10.0%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical progression</td>
<td>11.2%</td>
<td>19.0%</td>
</tr>
<tr>
<td>AUR*</td>
<td>8.1%</td>
<td>13.2%</td>
</tr>
<tr>
<td>Surgery*</td>
<td>4.8%</td>
<td>9.5%</td>
</tr>
<tr>
<td>Clinical progression†</td>
<td>10.2%</td>
<td>14.0%</td>
</tr>
<tr>
<td>AUR‡</td>
<td>7.0%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Surgery‡</td>
<td>5.0%</td>
<td>6.3%</td>
</tr>
</tbody>
</table>

Patients receiving 5ARIs early were less likely to have clinical progression than those receiving them late.

Early: patients receiving add-on 5ARI therapy on or within 30 days of index date.

Late: patients receiving add-on 5ARI therapy to baseline α-blocker therapy within a period of 30 days to 6 months following index date.
CombAT: Effect on IPSS and $Q_{\text{max}}$

Men with moderate symptoms, volume $\geq 30$ ml and PSA $\geq 1.5$ ng/ml:

- Combination therapy significantly improved symptoms versus either monotherapy – from 9 months versus tamsulosin – from 3 months versus dutasteride – sustained at 4 years

- Combination therapy significantly improved $Q_{\text{max}}$ – from month 3 versus tamsulosin monotherapy – from month 3 versus dutasteride monotherapy – sustained at 4 years

# Medical Treatment Comparison

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Onset</th>
<th>LUTS</th>
<th>Uroflowmetry (Q_{\text{max}})</th>
<th>Prostate size</th>
<th>PVR</th>
<th>Disease progression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conservative treatments</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watchful waiting, behavioural treatment</td>
<td>months</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>(\alpha)-adrenoceptor antagonists</td>
<td>days</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>- / +</td>
<td>+++ (symptoms)</td>
</tr>
<tr>
<td>5(\alpha)-reductase inhibitors</td>
<td>months</td>
<td>+</td>
<td>++</td>
<td>+ - ++</td>
<td>-</td>
<td>+++ (retention)</td>
</tr>
<tr>
<td>Muscarinic receptor antagonists</td>
<td>weeks</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>(storage symptoms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plant extracts</td>
<td>weeks</td>
<td>+</td>
<td>- / +</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>(\alpha)-adrenoceptor antagonists + 5(\alpha)-reductase inhibitors</td>
<td>days</td>
<td>++</td>
<td>++</td>
<td>+ - ++</td>
<td>- / +</td>
<td>+++ (symptoms + retention)</td>
</tr>
<tr>
<td>(\alpha)-adrenoceptor antagonists + muscarinic receptor antagonists</td>
<td>days</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>- / +</td>
<td>?</td>
</tr>
<tr>
<td>PDE5-inhibitors</td>
<td>weeks</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>?</td>
</tr>
</tbody>
</table>
Male LUTS – Medical Therapy

Male LUTS (without absolute indications for surgery)

- symptom bother, IPSS > ?
- nocturnal polyuria only?

- OAB - storage symptoms only?
- prostate volume > 40 ml?
- long-term treatment?

- Education + Lifestyle Advice with or without α₁-blocker
  - residual storage symptoms
  - Watchful Waiting with or without Education + Lifestyle Advice

- add Muscarinic Receptor Agonist with or without Education + Lifestyle Advice
- Education + Lifestyle Advice with or without 5α-Reductase Inhibitor ± α₁-blocker
- Education + Lifestyle Advice with or without Muscarinic Receptor Antagonist
- Education + Lifestyle Advice with or without Desmopressin

Case 1 - Again

- 64 year old male patient
- Seeking treatment with complaints of LUTS
- TRUS 48 ml, PVR: 64 ml, Qmax 10.4 ml/s, IPSS: 17/4

<table>
<thead>
<tr>
<th>What would you recommend, now?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Watchful waiting/LS-Advise</td>
</tr>
<tr>
<td>2. Phytotherapy</td>
</tr>
<tr>
<td>3. α-Blocker</td>
</tr>
<tr>
<td>4. 5-α-Reductase-Inhibitor</td>
</tr>
<tr>
<td>5. Combination-Therapy (3.+4.)</td>
</tr>
<tr>
<td>6. Surgery</td>
</tr>
</tbody>
</table>
Case 2.1

- 54 year old male patient
- Send from wife (frequent voiding)
- TRUS 24 ml, PVR: 20 ml, Qmax 19.8 ml/s, IPSS: 5/2
- Micturation: day: 2-3 x, night: 4-6 x

What would you do?

1. Start medical treatment
2. Additional diagnostics
3. Perform surgery
Case 2.2

Drink - Micturition Protocol:

- Fluid intake (08.00 – 16.00): 1 l of Coffee
- Fluid intake (16.00 – 22.00): 1.5 l of water
  0.5- 1 l beer

What would you recommend?

1. Watchful waiting/LS-Advise
2. Phytotherapy
3. α-Blocker
4. 5-α-Reductase-Inhibitor
5. Combination-Therapy (3.+4.)
6. Surgery
Case 3

- 60 year old male patient

- Seeking treatment with complaints of LUTS

- TRUS 28 ml, PVR: 45 ml, Qmax 12 ml/s, IPSS: 14/3

What would you recommend?

1. Watchful waiting/LS-Advise
2. Phytotherapy
3. α-Blocker
4. 5-α-Reductase-Inhibitor
5. Combination-Therapy (3.+4.)
6. Surgery
Case 4

- 60 year old male patient
- Seeking treatment with complaints of LUTS
- TRUS 45 ml, PVR: 45 ml, Qmax 12 ml/s, IPSS: 14/3

What would you recommend?

1. Watchful waiting/LS-Advise
2. Phytotherapy
3. α-Blocker
4. 5-α-Reductase-Inhibitor
5. Combination-Therapy (3.+4.)
6. Surgery
Case 5.1

- 60 year old male patient
- Seeking treatment with complaints of LUTS
- TRUS 52 ml, PVR: 120 ml, Qmax 7.5 ml/s, IPSS: 22/5, PSA: 3 μg/l

What would you recommend?

1. Watchful waiting/LS-Advise
2. Phytotherapy
3. α-Blocker
4. 5-α-Reductase-Inhibitor
5. Combination-Therapy (3.+4.)
6. Surgery
Case 5.2 – F/u at 6 month

- TRUS 45 ml (52)
- PVR: 110 ml (120)
- Qmax 9.5 ml/s (7.5)

IPSS: 17/3 (22/5)
PSA: 1.8 µg/l (3)

This is a successful treatment!

1. Agree
2. Disagree
Case 5.3 – F/u at 4 years - A

- TRUS 35 ml (52)
- PVR: 80 ml (120)
- Qmax 10.5 ml/s (7.5)
- IPSS: 14/2 (22/5)
- PSA: 2.0 μg/l (3)

Still a successful treatment!

1. Agree
2. Disagree
3. Have to do further diagnostics
Case 5.4 – F/u at 4 years - B

- TRUS 40 ml (52)
- PVR: 140 ml (120)
- Qmax 9.5 ml/s (7.5)

IPSS: 14/2 (22/5)
PSA: 1.6 μg/l (3)
Recurrent UTI/1 x AUR

Still a successful treatment!

1. Agree
2. Disagree
3. Add antibiotic prophylaxis
4. Counsel about surgery
Thorsten Bach
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