Canadian Undergraduate Urology Curriculum (CanUUC):
Prostate Diseases
LUTS/Benign Prostate Hyperplasia
Objectives

1. List the lower urinary tract symptoms (LUTS) found in men with BPH.
2. List the differential diagnosis of a man presenting with LUTS.
3. Outline the investigations required when evaluating a man with LUTS.
4. List the medical treatments of BPH.
5. List the indications for surgical treatment of BPH.
Benign Prostatic Hyperplasia

- Commonly associated with voiding & urinary storage symptoms

- Epidemiology
  - Extremely common with 70% of men in their 70’s describing voiding symptoms
Benign Prostatic Hyperplasia: Pathophysiology

- **Pathophysiology**
  - Prostate volume increases from puberty
  - Androgen dependant
  - Symptoms don’t always correlate with gland size
  - Static compression of the urethra
    - Glandular volume
  - Dynamic compression of the urethra
    - Smooth muscle component of prostate stroma

- Hypertrophied detrusor muscle
- Obstructed urinary flow
Lower Urinary Tract Symptoms (LUTS)

- **Storage Symptoms**
  - Frequency
  - Urgency ± urge incontinence
  - Nocturia

- **Voiding Symptoms**
  - Hesitency
  - Decreased stream
  - Straining to void
  - Incomplete emptying
  - Urinary retention
  - Overflow incontinence

*LUTS does not equate to BPH but BPH is the most common cause of LUTS*
Differential Diagnosis of LUTS

Multiple problems can co-exist

- **Pre-Prostatic Causes**
  - Stones/Tumors
  - Infections/inflammatory conditions
  - Neurogenic Bladder (spinal cord injuries, MS, Diabetes, etc)
  - Atonic Bladder /Overactive Bladder
  - Polyuria/Polydypsia

- **Prostatic Causes**
  - BPH
  - Prostatitis
  - Prostate Cancer (advanced)

- **Post-Prostatic Causes**
  - Urethral Stricture
  - Meatal Stenosis
Evaluation: Medical History

**Medical History**

- Should focus on:
  - Urinary tract symptoms
  - UTI, Hematuria
  - Previous surgery
  - Family history of prostate carcinoma
  - Co-morbidities/general health issues

- Medications
  - (Anti-cholinergics & sympathomimetics)

- Voiding diary (optional)
Evaluation: Physical Examination

Physical Examination

Complete exam including:

- Abdomen (assess bladder)
- External genitalia
- Focused neurological exam
- Digital Rectal Examination (DRE)
- (Assess for concurrent disease)
BPH: Recommended Investigations

1. Urinalysis and culture
2. PSA (if appropriate)
3. Serum Creatinine
4. IPSS (AUA symptom score)
American Urological Association Symptom Index (AUA-SI)

1) Incomplete bladder emptying
2) Frequency
3) Intermittency
4) Urgency
5) Weak stream
6) Straining
7) Nocturia

<table>
<thead>
<tr>
<th>AUA BPH Symptom Score</th>
<th>Not at all</th>
<th>Less than 1 time in 5</th>
<th>Less than half the time</th>
<th>About half the time</th>
<th>More than half the time</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2. Over the past month, how often have you had to urinate again less than two hours after you finished urinating?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3. Over the past month, how often have you found you stopped and started again several times when you urinated?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>4. Over the past month, how often have you found it difficult to postpone urination?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5. Over the past month, how often have you had a weak urinary stream?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>6. Over the past month, how often have you had to push or strain to begin urination?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?</td>
<td>None</td>
<td>1 time</td>
<td>2 times</td>
<td>3 times</td>
<td>4 times</td>
<td>5 or more times</td>
</tr>
</tbody>
</table>

Total Symptom Score

The Disease Specific Quality of Life Question
The International Prostate Symptom Score uses the same 7 questions as the AUA Symptom Index (presented above) with the addition of the following Disease Specific Quality of Life Question (either score) scored on a scale from 0 to 6 points (delighted to terrible).

*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?*
LUTS: Optional Investigations

- **Cystoscopy**
  - If urinalysis abnormal (hematuria or pyuria)
  - Patient <50 years old

- **Renal Ultrasound**
  - If serum Cr elevated

- **PVR urine/Uroflow**

- **Urodynamic’s**
  - Patient <50 years old
  - Atypical symptoms or neurologic disease
  - Incontinence (male)
LUTS: Treatment Options

1) Lifestyle Measures
2) Watchful Waiting
3) Medical Management
   a) Alpha blockers
   b) 5-alpha reductase inhibitors (5 AR’s)
4) Surgical Management
1. Treatment Options:
Lifestyle Measures

 Fluid modification
- Reduce fluid intake in the evening
- Avoid caffeine, alcohol

 Timed voiding

 Modify medications
- I.e: change time of dosing diuretics
- Avoid cold remedies
- Avoid anti-cholinergics
- Avoid alpha-agonists (i.e. decongestants)
Treatment Options: Herbal Supplements

**Herbal:** Commonly available OTC supplements

- Saw palmetto extract (Seronoa repens)  
  (Recent NEJM Paper cited no proven benefit)
- Pumpkin seed

**Mineral:**

- Zinc (however, no proven benefit)

2. Treatment Options: Watchful Waiting

**Watchful Waiting:**

- Patient monitored by physician without active intervention for LUTS
- Safe in patients with mild, stable symptoms
- Intervene when symptoms worsen or complications arise
3a. Medical Treatment: Long-acting Non-selective $\alpha_1$-blockers

- The prostate has a muscular component (centrally)
- These fibers are alpha-receptor mediated
3a. Medical Treatment: Long-acting Non-selective $\alpha_1$-blockers

**Long-acting non-selective $\alpha_1$-blockers:**
- Dosage is increased in a stepwise fashion at weekly intervals
- Does not affect PSA
- Acts to relax prostatic/bladder neck smooth muscle (& vascular smooth muscle - non selective)

- **Doxazosin** (Cardura)
  - Dosage: 1-2 mg OD, titrate up to 4-8 mg OD

- **Terazosin** (Hytrin)
  - Dosage: 1 mg OD, titrate up to 2, 5, or 10 mg OD
3a. Medical Management: Long-acting Selective $\alpha_{1A}$-blockers

**Long-acting selective $\alpha_{1}$-blockers**

- Relaxes the smooth muscle of the prostate and bladder neck
- Does not interfere with bladder contractility
- Does not affect PSA

- **Alfuzosin (Xatral)**
  - Dosage: 10 mg OD
  - No dose titration

- **Tamsulosin (Flomax)**
  - Dosage: 0.4 mg OD
  - $\alpha_{1A}$ receptor-selective
  - Option of safe higher dose of 0.8 mg
$\alpha_1$-Blockers: Side Effects

⇒ 5 known side effects of alpha blockade for LUTS

- Asthenia
- Hypotension
- Retrograde ejaculation
- Dizziness
- Flu like syndrome
3b. Medical Management: The 5-α-reductase Inhibitors

5-α-reductase inhibitors:
- Regulate androgen available to prostate
- Slow the rate of prostate enlargement
- Reduce prostate volume
- Reduce PSA by ~50%
- Takes 3-6 months to exert clinical effect
5-α-reductase Inhibitors

- Men with larger prostates (> 40 g) respond most favorably
- **Finasteride**
  - Dosage: 5 mg OD – type II inhibitor
- **Dutasteride**
  - Dosage: 0.5 mg OD – type I and II inhibitor
5 Alpha-Reductase Inhibitors: Side Effects

- Decreased libido 3-8%
- Ejaculatory disorder 1-5%
  (not always reversible)
- Erectile dysfunction 5-10%
  (not always reversible)
- Breast tenderness 1%
- Gynecomastia 1%
4. LUTS: Indications for Surgery

- Bothersome symptoms despite treatment
- Develop BPH-related complications
  - Urinary Retention
  - Bladder calculi
  - Recurrent UTI
  - Recurrent hematuria from the prostate
  - Upper tract dysfunction (hydronephrosis)
- Surgical approach will depend on:
  - Patient’s prostate size
  - Surgeon’s judgment
  - Patient’s co-morbidities
BPH Surgery:
Transurethral Resection of Prostate (TURP) is the Most Common Surgery for BPH

Transurethral resection of the prostate (TURP)
Standard of care
Uses electosurgery to “core” out the obstructive tissue
LUTS: Surgical Techniques

**TURP** - Transurethral Resection of Prostate
- Gold standard for surgical treatment of BPH if prostate has moderate size

**Minimally invasive surgeries**
- Numerous laser vapourization techniques

**Open prostatectomy when prostate is very large**

> 100cc
Complications:
TURP

- Retrograde ejaculation (very common)
- Incontinence
- Erectile Dysfunction
- Bladder neck Contracture/Urethral Stricture
- Risks of any Operation (Bleeding, UTI, etc.)
Treatment of BPH: Summary

⇒ **Watchful Waiting**
  - Patients with mild symptoms

⇒ **Alpha Blocker**
  - Relaxes prostatic smooth muscle
  - Rapid relief of symptoms (within 2 weeks)
  - Likely does not address eventual progression

⇒ **5-α-reductase inhibitor**
  - Decreases prostate volume
  - “Slower” acting (3-6 months)
  - May reduce risk of progression
  - More suitable for larger prostates
Prostate Cancer
Prostate Cancer Objectives

1. Discuss the pros/cons of early detection of prostate cancer.
2. How we diagnose prostate cancer
3. Talk about what PSA is and what causes it to be elevated.
4. Talk about basic treatment options for prostate cancer both early and advanced.
5. Recognize that spinal cord compression due to metastatic prostate cancer can occur
Prostate Cancer Statistics

- Most common non-cutaneous malignancy in men in North America
- 2nd most common cause of cancer-related deaths in men
- 1 in 7 men will be diagnosed
- Lifetime risk of being diagnosed with prostate cancer is 18% but risk of dying of prostate cancer is only 3%
Prostate Cancer
Risk Factors

Established
- Advancing age
- Presence of androgens
- Family history
- African ancestry

Potential
- High dietary fat?
- Vitamin D or E deficiency?
- Selenium deficiency?
Prostate Cancer: Presentation

- **Early stages usually asymptomatic**
  - Most cases detected by serum PSA screening
  - Palpable nodule or firmness on DRE

- **Advanced stages**
  - Urinary retention/renal failure
  - Bone pain
  - Anemia
  - Weight loss, fatigue
  - Spinal cord compression
Goal

To identify the presence of disease at a stage when treatment can be given that will cure it

Use a combination of DRE and PSA
Digital Rectal Examination

- DRE (digital rectal exam) has a 50% positive predictive value
- DRE alone is not a good screening tool
- BUT it is an important part of screening
What is PSA (Prostate Specific Antigen)?

- A Serine protease (enzyme) found in the prostate
- Secreted by prostate epithelial cells
- Found in ejaculate
- As diagnostic tool for:
  - Screening
  - Staging
  - Prognostic indicator
  - Surveillance
Prostate Cancer: Screening with PSA

⇒ No clear cut-point between normal and abnormal PSA levels. Even PSA cut-off of 1.1 ng/ml misses up to 15% of prostate cancer (The Cancer Prevention Trial – 2003)

⇒ Positive predictive value for PSA > 4ng/ml = 30% (i.e. About 1 in 3 men with elevated PSA have prostate cancer detected at time of biopsy)

⇒ PPV increases to 45-60% for PSA > 10ng/ml

⇒ Nearly 75% of cancers detected in the grey zone (PSA 4-10) are organ confined; potentially curable.

⇒ <50% of prostate cancers organ confined if PSA >10
Prostate Cancer Screening: Pros and Cons

⇒ **Pros**

- Early detection of disease leads to higher cure rates
- By the time symptoms of prostate cancer present usually not curable
- **Screening offers a modest effect on mortality**
- The “number needed to screen” is similar to studies on mammography for Breast Ca and fecal occult blood testing for Colon Ca

⇒ **Cons**

- If tests abnormal, need for prostate biopsy
- If cancer found & treatment chosen, morbidity from therapy
- If insignificant cancer found, treatment was unnecessary
- Risk of overdiagnosis, overtreatment
Screening Recommendations

Discuss with the patient and if he decides to be screened

- Annual PSA and DRE
- Age 50-70 yrs (with at least 10 yr life expectancy)
- Begin screening at age 40 if risk factors
  - African ancestry
  - First degree relative(s) with prostate cancer

*A shared decision-making approach to PSA screening seems most appropriate*
Causes of an elevated PSA

1. Prostate cancer
2. Age
3. Prostate size (BPH)
4. Infection/inflammation
5. Recent instrumentation (biopsy, catheterization, etc)
6. Physiological variation
   - Recent ejaculation
Free/Total PSA Ratio: A Way to Improve Specificity

- Prostate cancer maybe associated with more protein-bound PSA (less free PSA) than in BPH
  - F/T ratio is lower in patients with prostate cancer
  - Can improve test specificity
  - Useful when total PSA in 4-10 ng/ml range
Prostate Cancer: Diagnosis

- Indications for transrectal ultrasound (TRUS) guided biopsy
  - Palpable nodule on DRE
  - Elevated serum PSA
- Biopsy involves 10-18 needle cores taken mostly from the peripheral zone of the prostate
- Transrectal ultrasound alone/CT scan/MRI not sensitive enough to make the Diagnosis
Prostate Cancer: Pathology

- Adenocarcinoma
- Gleason “grade” is from 1-5 based on glandular architecture
- Gleason score is the total primary grade (1-5) + secondary grade (1-5) = 2-10
  - 4-6/10=well-differentiated
  - 7/10=moderately differentiated
  - >8/10=poorly differentiated

Gleason's Pattern Scale

1. Small, uniform glands.
2. More space (stroma) between glands.
3. Distinctly infiltration of cells from glands at margins.
4. Irregular masses of neoplastic cells with few glands.
5. Lack of or occasional glands, sheets of cells.
Prostate Cancer: Staging

- Can spread to adjacent organs (seminal vesicles, bladder), lymph nodes, bone
- Most bone mets are **osteoblastic**
- Prior to initiating treatment consider
  - Bone scan (PSA>10, Gleason Score >7)
  - CT scan pelvis/abdomen (PSA >10, Gleason Score >7))
- These tests are typically not required in asymptomatic men with low risk prostate cancer
Prostate Cancer Treatment

Considerations

- Patient’s age
- Co-morbid health conditions
- Tumor stage
- Tumor grade (Gleason score)
- Often a patient choice
- Surgery and
Early Stage Prostate Cancer

Early stage Cancer

1. Radical Prostatectomy
2. External Beam Radiotherapy
3. Radioactive Seeds (Brachytherapy)
4. Active Surveillance
5. Observation – Watchful Waiting
Prostate Cancer Treatment:
1. Radical Prostatectomy

- Radical Prostatectomy
  - Complete surgical removal of entire prostate, seminal vesicles
  - Considered a good treatment for men <70 years of age with clinically organ confined cancer who are healthy
  - Open or laparoscopic/robotic approaches
Prostate Cancer Treatment:
1. Radical Prostatectomy
Complications of Radical Prostatectomy

- <10% risk of blood transfusion
- Wound infection
- Rectal injury
- Urinary incontinence
- Erectile dysfunction
- Anesthetic related
Prostate Cancer Treatment: Radiotherapy

Radiotherapy Options
- External Beam
- Brachytherapy (seed implant)
- Concept of maximizing dose to the tumor and minimizing collateral damage

Curative options for patients at high risk for morbidity from radical prostatectomy
- Age, medical co-morbidities
- Patient preference
Prostate Cancer Treatment:

2. External Beam Radiotherapy
Complications of Radiation for Prostate Cancer

External Beam Radiation Therapy
- Hematuria
- Radiation proctitis
  - Loose, bloody stools
- Urinary retention
- Strictures (urethra and ureter)
- Erectile dysfunction
- Secondary malignancies
  - Bladder, rectal, hematological
Prostate Cancer Treatment:
3. Brachytherapy
Complications of Brachytherapy for Prostate Cancer

- Urethral strictures
- Seed migration
- Urinary retention
- Erectile dysfunction
- Irritative voiding symptoms
Prostate Cancer Treatment:

4. Active Surveillance

⇒ Observing low grade tumors in men <70 yrs and >10 yr life expectancy
⇒ Delay definitive treatment until it is necessary and cancer is still curable
⇒ Goal is to delay potential treatment-related morbidity
⇒ Monitor DRE, PSA, and periodic repeat biopsy
⇒ Ideal candidate:
  ○ PSA < 10
  ○ Normal DRE
  ○ Gleason <7 (low grade)
  ○ Only 1-3 / 12 biopsy cores positive
Prostate Cancer Treatment:  
5. Watchful Waiting

- Observing low grade tumors in men >70 yrs or <10 yrs life expectancy
- Institute hormonal therapy when patient becomes symptomatic
- No curative intent
Advanced or Metastatic Prostate Cancer

- Not curable disease
- Goals shift to disease control
- Development of cancer cells unresponsive to androgen deprivation
- Typically occurs slowly over time, although it can occur rapidly
Advanced Prostate Cancer: Treatment

- Androgen Deprivation (Hormonal Rx)
  - Orchidectomy
  - LHRH analogues
  - Antiandrogens

- Supportive therapies
  - Analgesics
  - Steroids
  - Bisphosphonates/Vitamin D/Calcium for bone health

- Chemotherapy
  - Taxotere, Docetaxel
  - Last line of treatment
Charles Brenton Huggins (1901–1998)

- Only Canadian-born doctor ever to receive the Nobel Prize in Physiology or Medicine.
- Nobel Prize received in 1966.
- For his discoveries concerning hormonal treatment of prostatic cancer.
- Born in Halifax, Nova Scotia.
  B.A (Acadia)

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Osteoblastic Bone Metastases
Metastatic prostate cancer is a common cause of spinal cord compression

- Clinical recognition is critical
- Signs and symptoms
  - Back pain
  - Neurological symptoms in saddle distribution
  - Lack of rectal tone, fecal and urinary incontinence
  - Paraplegia below the level of compression
- MRI is diagnostic
Spinal Cord Compression

Treatment
- Emergency decompression laminectomy by spinal surgeons
- Emergency radiation to affected level
- Dexamethasone/steroids
- Emergency bilateral orchidectomies if patient not already on androgen deprivation
Prostate Cancer
Prognosis

- Depends upon grade, stage and treatment
- Early stage/well-differentiated Ca treated by radical prostatectomy:
  - 85% + 10 year survival
- Metastatic disease
  - <10% 5 year survival
Prostate Cancer Prevention

➡️ Modifiable Factors

○ Diet
  ■ Saturated fats
  ■ Red Meat
  ■ BBQ meats

○ Lifestyle
  ■ Exercise

○ Drug therapy
  ■ 5α reductase inhibitor
  ■ Vitamin D
Prostate Cancer Prevention

- Two major studies using $5 \alpha$ reductase inhibitors vs placebo
- Similar reduction in prostate cancer diagnosis in the treatment arms (23-24%)
- Not currently approved by Health Canada for prostate cancer prevention
- PCPT (Thompson et al NEJM 2003)
  - Finasteride
- Reduce (Andriole et al NEJM 2010)
  - Dutasteride
Prostate Cancer Prevention

่อ Problems
- Potential for the development of high risk prostate cancer
- Expensive
- Sexual/ejaculatory dysfunctions side effects may be occur and aren’t always reversible
- Long time to see the results of prevention
  - 10-20 years