The Underactive Bladder
Michelle J. Lajiness FNP-BC
Nurse Practitioner Urology
Beaumont Health System - Royal Oak, Michigan

Objectives

• Define Underactive Bladder (UAB)
• Discuss Current Treatment for UAB
• Describe New Therapy for UAB

Why Have We Not Noticed the Elephant?
Aging Bladder

The Problem

- Bladder contractility and voiding efficiency (sphincter relaxation) diminish with age
- The health and independence of older people is impacted by lower urinary tract symptomology
- Loss of bladder control is the second most common reason for nursing home placement of the elderly
- UAB is not discussed or well known
- Patients are misdiagnosed and many times treated incorrectly
- OAB to UAB theory
The Problem

• Worldwide more than 200 million people experience urinary incontinence
• That number is expected to grow as America’s baby boomers age.
• Current statistics indicate that urinary incontinence is a $4 billion financial burden on our health system
• Urinary incontinence can be a result of underactive bladder

The Other Bladder Syndrome: Underactive Bladder

Aging
Diabetes mellitus (diabetic cystopathy)
Bladder outlet obstruction (BOO)
Idiopathic
Neurological disorders
• SCI, Cerebrovascular accidents, MS, Parkinson’s disease
• Injury to the spinal cord, cauda equina, and pelvic plexus
• Pelvic surgery and fractures, Herniated disc, Pudendal nerve injury
• Infectious neurologic problems
• AIDS, Neurosyphilis, Herpes zoster+simplex, Guillain-Barré syndrome

CURE UAB – First International Congress of Urologic Research and Education on Aging Underactive Bladder

• Feb 2014
• Purpose
  • Establish a definition
  • Discuss research findings
  • Promote collaborations
  • Enhance understanding and awareness
• Brought together
  • Clinicians
  • Educators
  • Researchers
  • International participants
Results of 2014 CURE UAB

- Public and private collaboration toward public awareness campaign of the medical, social and financial burden of UAB
- Consensus definition of UAB and working UAB classification with questionnaire to help screen and diagnose UAB
- Detailed epidemiologic surveys of UAB
- Health economics of UAB and complications arising from UAB
- Advance the understanding in basic pathophysiology of UAB
- Track bladder emptying with age to determine When, Where, and How to Intervene
- Develop new and better interventions that incorporate the diverse needs of UAB population

International Continence Society Definition: Detrusor Underactivity

- “a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying, and/or failure to achieve complete bladder emptying within a normal time span”
- DU is a urodynamic diagnosis based on pressure-flow study
- ICS definition also implies that DU is associated with urinary signs, that is, prolonged bladder emptying time and/or post-void residual urine

National Library of Medicine
2009 MeSH: Urinary Retention

- Inability to empty the urinary bladder with voiding (urination)
ICD-9_CM Diagnosis Code 788.2 Retention of Urine

- Incomplete emptying of the bladder
- Accumulation of urine within the bladder because of inability to urine

Overactive Bladder as main subject at NIH.gov

Several items appear including:

Overactive bladder is defined by the International Continence Society as a syndrome of urinary frequency and urgency, with or without urge

Underactive Bladder as main subject at NIH.gov

Many topics come up pertaining to lower urinary symptoms

Definitions of over active bladder also appear.
OAB Definition: Urgency, with or without urge incontinence, usually with frequency and nocturia

Underactive Bladder Definition: Urinary symptoms including hesitancy, straining and incomplete bladder emptying in the absence of anatomic obstruction

Urinary Retention
Definition: The state in which the individual experiences incomplete emptying of the bladder. High urethral pressure inhibits voiding until increased abdominal pressure causes urine to be involuntarily lost, or high urethral pressure inhibits complete emptying of the bladder

The Underactive Bladder Foundation
Current Definition-Underactive Bladder

• Chronic bothersome inability to empty the urinary bladder

Primary UAB Outcome Parameter:
• Persistent residual urine volume >200 mL with bothersome symptoms
Neurgenic Bladder compared to UAB (MY clarification)

**Neurgenic**
- a dysfunction of the urinary bladder due to disease of the central nervous system or peripheral nerves involved in the control of micturition

**Causes**
- spinal cord diseases or injury
- neural tube defects including spina bifida
- brain tumors and other disorders of the brain
- peripheral nerve disease

**UAB**
- failure of the detrusor muscle to generate enough of a contraction to empty the bladder

**Causes**
- myogenic causes with impaired contractility from structural changes within the detrusor muscle and/or axonal degeneration demonstrated in unobstructed human bladders

Now UAB VS NEUROGENIC after CURE UAB

More questions than answers!!!!

UAB is a large umbrella

Under the umbrella
- Neurogenic bladder
- Constellation of symptoms
- Functional Obstruction (Not BOO)
- Impaired bladder emptying
- Bladder areflexia
- Overflow incontinence

DRAFTS: The Underactive Bladder Foundation

**Definition—Underactive Bladder**

Non-obstructive, urinary symptoms including hesitancy, and/or straining with co-existing partial or complete urinary retention

Urinary symptoms including hesitancy, straining and partial or complete urinary retention in the absence of anatomic obstruction

Urinary symptoms including hesitancy, straining and incomplete bladder emptying in the absence of anatomic obstruction
What is Underactive Bladder (UAB)?

Urinary incontinence is often thought of as the inability to hold in urine because of a weak or damaged sphincter or an overactive bladder. In fact, urinary retention or the inability to completely empty the bladder can also lead to bothersome urinary symptoms and incontinence. This is also known as underactive bladder or UAB.

Although underactive bladder is a common health problem in seniors, there is a lack of clarity, understanding and standardization of the term underactive bladder.

This condition occurs in both men and women and may be attributed to many diseases including aging, prostate enlargement and diseases that affect the nervous system including diabetes, multiple sclerosis and spinal cord injury.

Existing therapeutic strategies leave much to be desired. Patients with the condition may need to use catheterization in order to drain the bladder. There is no effective drug treatment currently. UAB has no cure and has not received adequate research funding support.

Causes of Urinary Retention

- Outlet obstruction
  - Intrinsic factors: obstructing prostate gland, bladder neck contracture, dyssynergic sphincters, foreign bodies
  - External factors such as fecal impaction and prolapsing pelvic organ

- Failure of detrusor
  - Detrusor underactivity UAB
  - Detrusor hyperactivity with impaired contractility
**UAB- Urinary Retention**

**Urinary Retention**
- Acute urinary retention
  - Urgency to void
  - Suprapubic pain or pressure
  - Inability to void
  - May or may not have dribbling.
- Chronic urinary retention
  - Voiding with or without LUTS
  - No pain or discomfort
  - Over distended bladder by PE, US or other tests
  - May or may not have overflow incontinence.

**UAB-Urinary Retention**

**Partial urinary retention**
- May or may not have LUTS
- Voiding with "high" residual urine
- Discovered as part of evaluation for incontinence, UTI, etc.
- This topic deserves further focused research and analysis.

**Management of Urinary Retention in the Elderly**
- Provide immediate relief with indwelling Foley.
- Monitor for possible diuresis and hematuria, and treat appropriately.
- Screen for extrinsic factors such as fecal impaction and incarcerated pelvic organ prolapse.
- Screen upper tracts for hydrenephrosis and measure renal function.
- Screen for drugs that could contribute to retention and discontinue if possible.
- For men, start an alpha blocker if patient can tolerate.
Management of Urinary Retention in the Elderly

Success rate for trial voiding after several days of Indwelling Foley

- Catherization alone – 48% (1)
- Catherization and alpha blocker – 62% (2)
- Other report with and without pharmacologic therapy – 58% - 84% (2)
- Maintain pharmacologic therapy
  - Alpha blocker
  - 5 alpha reductase inhibitor

Predictor of failure: Initial residual urine volume of 1,000 ml or more


Management of Urinary Retention

Failed trial voiding one or more times, candidate for definitive therapy?

- Ensure a well prepared patient with full perioperative care.
- Choose a procedure that will provide
  - Prompt effectiveness for voiding
  - Safety
  - Shortest hospital stay possible
  - Minimal after care
  - Least costly

Nursing Considerations

- Environmental assessment
  - Family support
  - Physical environment
- Patient Education
  - Signs symptoms
  - Causes
  - Tests
  - Treatment goals
  - Treatment options
- Cognitive assessment
  - Ability to follow instructions
- Functional assessment
  - Impaired mobility
Current Treatment Goals

Relieve Symptoms and prevent complications

Current Treatment Options

- Behavioral Therapy/Lifestyle changes
  - Fluid control
  - Monitoring triggers (caffeine intake)
- Catheters
- Diapers
- Medications
  - Urecholine (Bethanechol)
Aikens-Diokno Center of Urologic Research Excellence in Aging Underactive Bladder CURE-UAB

Mission: Develop basic research discoveries to viable externally funded clinical trials

Goal: To Become a world leader in creating and using knowledge that optimizes and enhances the management of age associated genito-urinary disorders

Future Treatments
Definitions

● Autologous Muscle-Derived:
Cells from the study participant’s (thigh) muscle are injected into their own body

● Stem Cells: Master cells that are able to divide and reproduce endlessly or grow into any one of the body’s more than 200 cell types.

Study Purpose

To identify the safety and potential effectiveness of autologous muscle derived-cells (MDCs) in the treatment of UAB.

Primary Outcome Measures

- Safety
  - Urologic function
  - Adverse events
Potential Risks
- Pain/discomfort
- Bleeding
- Infection
- Swelling
- Bruising
- Scarring
- Urinary complications

Secondary Outcome Measures
- Effectiveness
  - Urodynamics
  - Post Void Residual
  - Number of catheterizations vs voids
  - Quality of Life

Cell Process
1. Muscle Biopsy
2. Muscle Derived Cells
3. Culture
4. Autologous Injection
Muscle Biopsy

Certified shipping container for sending the muscle biopsy to lab at 4°C and for returning the product to the clinical site on dry ice

150 Million MDCs
Results of 1st FDA approved compassionate use

- 79 y o male who had not urinated for over 20 years
- 3 months after treatment cystometric capacity from 844 to 633
- No complications were noted
Next Steps

- Single center FDA approved 20 patient study
- Inclusion Criteria
  a. Males and females, at least 18 years of age
  b. History of UAB for at least 6 months documented in the medical record
  c. Recurring UAB symptoms
  d. Subjects unresponsive to relief symptoms of UAB with previous use of medications and/or other treatments
  e. Voiding difficulty (complains of difficulty emptying the bladder)
  f. Post void residual > 150 mL
  g. Total UAB Questionnaire Score > 3
  h. Females of child-bearing potential agree to use a reliable form of birth control for the entire study duration
  i. Willing and capable of understanding and complying with all requirements of the protocol, including proper completion of the voiding diaries and self-administered questionnaires

Next Steps Continued

- Exclusion criteria
  a. Pregnant, plans to become pregnant or lactating
  b. History of bleeding diathesis, uncorrectable coagulopathy, or would refuse a blood transfusion
  c. Currently on anticoagulant therapy
  d. Obvious neurological impairment
  e. Known allergy or hypersensitivity to bovine proteins or allergens, gentamicin sulfate, or ampicillin that medically warrants exclusion as determined by the physician
  f. Simultaneously participating in another investigational drug or device study or use of any investigational drug(s) or therapeutic device(s) within 3 months preceding enrollment
  g. Has been treated with an investigational device, drug, or procedure for UAB within the last 6 months.
  h. Medical condition or disorder that may limit life expectancy or that may cause protocol deviations (e.g. unable to perform self-evaluations and/or accurately report medical history, urinary symptoms, and/or data)
  i. History of cancer in pelvic organs, ureters, or kidneys or any cancer that has undergone treatment within the past 12 months
  j. Compromised immune system due to disease state, chronic corticosteroid use, or other immunosuppressive therapy
  k. History of radiation therapy to the bladder
Next Steps Continued

Exclusion Criteria

l. Tests positive for Hepatitis B (Hepatitis B Surface Antigen [HBsAg]), Hepatitis C (Anti-HCV test enzyme immunoassay [EIA]), and/or HIV
m. Abnormal renal function
n. An active urinary tract infection as evidenced by positive urine culture
o. Taking medication(s) that affect urination (e.g., medically necessary, stable drugs) such as prescription drugs, over-the-counter drugs, or dietary supplements, including herbal supplements and those taken with teas
p. Requires concomitant use or treatment with immunosuppressive agents
q. Pelvic organ prolapse beyond the introitus (e.g.,

Next Steps

Potential Patients

Contact Deborah Hasenau, RN- Study Coordinator

248-551-3565
Why Liposomes?

- Empty liposomes have been used to improve wound healing & barrier function of broken skin
- Most consistent finding in IC is a compromised bladder barrier function
- Liposomes have long history of safe clinical use
Liposomes for Interstitial Cystitis

Completed FDA Expanded Use Trial

- 14 patients enrolled; 11 women and 3 men; Average age 58 years (37-75)
- No treatment-related AEs or side effects were reported

<table>
<thead>
<tr>
<th>Weeks post-treatment</th>
<th>Mean</th>
<th>SEM</th>
<th>Median</th>
<th>IQR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain VAS</td>
<td>-2</td>
<td>0.62</td>
<td>-1.45</td>
<td>(-3.82, 0.00)</td>
<td>0.0073</td>
</tr>
<tr>
<td>8</td>
<td>-1.14</td>
<td>0.17</td>
<td>-0.55</td>
<td>(-3.90, -0.90)</td>
<td>0.2083</td>
</tr>
<tr>
<td>Urgency VAS</td>
<td>-1.51</td>
<td>0.44</td>
<td>-1.34</td>
<td>(-3.02, 0.00)</td>
<td>0.0029</td>
</tr>
<tr>
<td>8</td>
<td>-1.51</td>
<td>0.57</td>
<td>-1.25</td>
<td>(-3.38, -0.40)</td>
<td>0.012</td>
</tr>
<tr>
<td>ICSI + ICPI</td>
<td>-4</td>
<td>-4</td>
<td>(-7.00, -1.00)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>-4</td>
<td>-4</td>
<td>(-8.00, -1.00)</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>
There are millions of people in the US who are cancer survivors. Many say that they felt they had lots of support during their treatment, but once it ended, it was hard to make a transition to a new way of life. It was like entering a whole new world where they had to adjust to new feelings, new problems and different ways of looking at the world.

Survivorship
Hemorrhagic cystitis after Radiation and Chemotherapy
- A new normal
- Follow-up medical issues
- Physical changes
- Family issues

Hemorrhagic Cystitis
- HC is a condition characterized by recurrent hematuria, urinary urgency and supra pubic pain related to chemotherapeutic agents and pelvic radiation
- Rare and serious disease, 2-4% bleed to death
- Existing treatment options are inadequate with no approved pharmacotherapy
- Prevalence is within the FDA definition of Rare Diseases Orphaned disease 60,000

Modeling Radiation Cystitis

Changes resulting from radiation injury involving bladder. Changes are seen in bladder of male patient with advanced transitional cell carcinoma of bladder before and after external beam radiation.
Tacrolimus

- Tacrolimus is a potent hydrophobic immunosuppressive agent that hinders IL-2-dependent T-cell activation by inhibiting calcineurin phosphatase.
- Systemic administration of tacrolimus is limited by the high incidence of adverse effects including nephrotoxicity and hypertension.
- Positive proof of concept in rat model of sterile hemorrhagic cystitis.

Management of Hemorrhagic and Radiation Cystitis

- Translational research toward clinical trial.
- Established CPT code for simple intravesical instillation.
- Intravesical liposome-tacrolimus can be used in moderate and severe hemorrhagic and radiation cystitis to decrease risk of mortality and maximize efficacy.

Urine Biomarker

A molecular indicator of a specific biological property; a biochemical feature or facet that can be used to measure the progress of disease or the effects of treatment.
The Julie R. and Robert S. Taubman Urology Research Fund has provided the funding for this important IC research project. Without the Taubman’s generosity, this research would not be possible.