What is Nocturia?
- Nocturia is the complaint that the individual has to wake at night one or more times to void. (ICS definition from ICS Standardization of Terminology Report 2002)
- Each void is preceded and followed by sleep.

When voiding occurs during sleep
Nocturnal Enuresis

For frail elderly who wake with the need to void but unable to reach the toilet before voiding
Nocturia + Incontinence

How Common is Nocturia?
- Telephone survey on 22,979 subjects in HK in 2003 HKU & HKUA found 46.7% people have nocturia.
- The prevalence of nocturia increased with advancing age (58% of women and 64% of men 51-60 years and 61% of women and 81% of men over 70 years are suffering from nocturia).

What are the Consequences of Nocturia?
- Main cause of disturbed sleep maintenance (67% overall, >70% if age >70) in the community.
- Nocturia that occurs twice or more per night can have a substantial adverse effect on the patient’s quality of life (QOL).
- Greater incidence of Falls & Fractures.
- Higher Mortality.
What are the Causes of Nocturia?

Nocturia

- Polyuria
- Bladder capacity
- Mixed

Global Polyuria
- Nocturnal Polyuria

Global Low Bladder Capacity

Causes of Global Polyuria:

- Diabetes mellitus
- Diabetes insipidus
- CRF or renal insufficiency
- HyperCa, HypoK
- Habitual or Psychogenic polydipsia
- Drugs (e.g. diuretics)
- Tea, Caffeine, Alcohol, soft drinks

Global Poluria
- 24-hr urine volume >40ml/kg.
  (e.g. 50kg, if urine >2L in 24 hr => polyuria)
- Both day & night urinary frequency but near normal voided volume.

Causes of Global Poluria:

A. Space occupying lesion inside bladder:
   - Bladder tumors - 1º or 2º.
   - Large bladder stone.
B. External compression
   - Pregnancy
   - Pelvic tumour (1º or 2º)
   - Faecal impaction

Nocturnal Polyuria

- Defined as production of an abnormally large volume of urine during sleep.
- Nocturnal Polyuria Index (NPI) = nocturnal urine volume / 24 hr urine volume.
- NPI is age-dependent:

<table>
<thead>
<tr>
<th>Age</th>
<th>Normal NPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-35</td>
<td>&lt;20%</td>
</tr>
<tr>
<td>36-60</td>
<td>(&lt;30-33%)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>≥33%</td>
</tr>
</tbody>
</table>

- Nocturnal urine volume >6.4ml/kg.
- Nocturnal diuresis >0.9ml/min.

Nocturnal Polyuria

- Defined as production of an abnormally large volume of urine during sleep.

Causes of Nocturnal Polyuria:

1. Peripheral edema with fluid re-distribution:
   - CHF, CRF, Cirrhosis, Nephrotic syn.
   - Autonomic system dysfunction
   - Vasodilator drugs (e.g. Ca antagonists)
   - Pregnancy
2. Circadian defect in secretion or action of ADH
   - Primary (Idiopathic): aging, stroke, CNS disorders
   - Secondary: Excessive evening intake of fluid, caffeine, alcohol
3. High Atrial Natriuretic Peptide Level during sleep
   - Obstructive Sleep Apnea
4. Long hours spent on beds

Global Low Bladder Capacity

- Both day & night urinary frequency with low voided urine volume.

Causes of Global LBC:

A. Less distensible bladder wall
   - Agering effect: slight decrease bladder capacity with increasing age.
   - Bladder wall lesions: Bladder tumors.
   - Low compliance bladder
   - Hyperreflexal bladder, chronic outflow obstruction, T.B, post-irradiation, interstitial cystitis, etc.
   - Unstable bladder contractions
   - Detrusor Overactivity (Idiopathic, Neurogenic)
   - Inflammation
   - UTI, interstitial cystitis, prostatitis, atrophic vaginitis & urethritis, post-irradiation cystitis, etc.
   - Invasive Masses
     - Bladder stone, CA bladder, BPH, CA prostate, foreign bodies.
   - Drugs with cholinergic effects, stimulant laxatives, etc.
   - Caffeine (coffee, cola, tea, chocolate).
   - Too concentrated urine due to too little fluid intake.
Global Low Bladder Capacity

Causes of Global LBC:

D. Reduced bladder size
   - Partial or total cystectomy
E. Functional low bladder capacity due to high post-voided residual volume (PVR)
   - Bladder outlet obstruction
   - BPH, CA prostate, urethral stricture, CA urethra
   - Detrusor-sphincter dyssynergia
   - Detrusor Underactivity (impaired detrusor contractility)
   - Nerve injury: birth trauma, rectal operation, cauda equina, DM autonomic neuropathy, etc.
   - Drugs with anti-cholinergic S/E: narcotics, cough medicine, Parkinsonism drugs, anti-psychotics, anti-depressants, etc.
F. Psychogenic
   - Anxiety, Obsessive behavior, etc.
   - Adaptive behavior to prevent urinary incontinence.

Nocturnal Low Bladder Capacity

Causes of Nocturnal LBC:

1. Idiopathic nocturnal detrusor overactivity
2. Primary Sleep Disorders
   - Insomnia
   - Obstructive & central sleep apnea syndrome
   - Periodic Limb Movement Disorder
   - Restless Leg Syndrome
   - Parasomnias
   - Sleep disorders related to medical diseases
     - e.g. COPD, cardiac diseases, etc.
   - Sleep disorders related to neurological diseases
     - e.g. Alzheimer's, Parkinson's diseases, nocturnal epileptic seizures, etc.

Prevalence of Different Types

Weiss et al reviewed 194 consecutive patients with nocturia (Neurourol Urodynam 1998; 17:467-72):

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturnal Polyuria (NP)</td>
<td>7%</td>
</tr>
<tr>
<td>Nocturnal LBC</td>
<td>57%</td>
</tr>
<tr>
<td>Mixed (NP + NLBC)</td>
<td>36%</td>
</tr>
<tr>
<td>(Global Polyuria)</td>
<td>23%</td>
</tr>
</tbody>
</table>

Summary of the Assessment from Bladder Diary

24 hr urine >40ml/kg
NPI >20-33%
NBCi >0 (nocturnal voided volume < max voided volume)

Example 1

- From Bladder Diary:
  - 24 hr urine volume = 1,500ml
  - Nocturnal urine volume = 750ml
- NPi = 750/1,500 = 50% (>33%)

Nocturnal Polyuria
Example 2
- 24 hr urine volume = 5,000ml
- Nocturnal urine volume = 1,500ml
- NPi = 1,500/5,000 = 30% (normal)
- Max voided volume = 500ml
- Nocturia Index (Ni) = 1,500/500 = 3
- Predicted nocturnal voids (PNV) = Ni – 1 = 3 – 1 = 2
- Actual nocturnal voids (ANV) = 2
- Nocturnal Bladder Capacity Index (NBCi) = ANV – PNC = 2 – 2 = 0 (nocturic voids at capacity)

Example 3
- 24 hr urine volume = 2,500ml
- Nocturnal urine volume = 750ml
- NPi = 750/2,500 = 30% Global LBC
- Max voided volume = 150ml
- Nocturia index (Ni) = 750/150 = 5
- Predicted nocturnal voids (PNV) = Ni – 1 = 5 – 1 = 4
- Actual nocturnal voids (ANV) = 8
- Nocturnal Bladder Capacity Index (NBCi) = ANV – PNV = 8 – 4 = 4

Example 4
- 24 hr urine volume = 2,500ml
- Nocturnal urine volume = 1,500ml
- NPi = 1,500/2,500 = 60% Nocturnal Polyuria
- Max voided volume = 500ml
- Nocturia Index (Ni) = 1,500/500 = 3
- Predicted nocturnal voids (PNV) = Ni – 1 = 3 – 1 = 2
- Actual nocturnal voids (ANV) = 6
- NBCi = ANV – PNV = 6 – 2 = 4 Nocturnal LBC

Nocturnal Polyuria + Nocturnal LBC

Management of Nocturia
1. Treat underlying condition first
2. General measures
3. Pharmacologic treatment

1. Treat Underlying Conditions
- DM, DI
- CHF
- OSA
- Drug-induced (diuretics, drugs with anti-cholinergic S/E, etc.)
- OAB
- High PVR
- ......

2. General Measures
- Fluid Intake
  - Reduce fluid intake (esp. 4-6 hr before sleep) in those who drinks too much before sleep.
  - Report stated that nocturnal polyuria was not improved simply by limiting water intake.
  - Risk development or exacerbation of dehydration-induced cerebral infarction who already drinks little.
  - Recommended: daily water intake will generally result in a 24-hr urine volume of 10-15 mL/kg.
- Avoid caffeine/ alcohol intake.
- Exercise therapy in the evening or at night
  - Pumping action of the muscles return accumulated interstitial fluid to the blood vessels and that some excess water is also removed as sweat.
  - Exercise is also effective in relieving stress, which can be related to sleep disorders.
  - No RCT to prove it.
- Reduce edema
  - Compression stockings.
  - Daytime nap of 30 min with the feet elevated.
  - No RCT to prove it.
3. Pharmacologic Treatment

Drugs acting on kidney
- Desmopressin to increase water reabsorption during sleep
- Diuretics to remove excess water before sleep

Drugs acting on bladder
- Anti-muscarinic agents to reduce overactive bladder
- Cholinergics for detrusor underactivity

Drugs acting on urethra & prostate
- α-blockers for BPH
- 5α-reductase for BPH

Desmopressin

Formulations:
1. Intranasal spray (10 mcg/spray):
   - Start 1-2 spray nocte.
   - Max dose 40 mcg nocte.
2. Oral tablet (0.1 mg, 0.2 mg):
   - Start 0.1 mg nocte.
   - Max 0.4 mg nocte.
3. SL Melt (60, 120, 240 mcg melt tab):
   - Start 60-120 mcg nocte.
   - Max 240 mcg nocte.

Desmopressin

- Synthetic analogue of the anti-diuretic hormone (vasopressin).
- Selective V2 receptor agonist increases water reabsorption in the renal collecting ducts and the ascending limb of Henle's loop, reducing urine volume and increasing urine osmolality.
- The antidiuretic effects are 3-10 folds greater than vasopressin.
- Minimal vasopressor activity (poor affinity for V1 receptor).
- Proven benefit in treatment of polyuria:
  - Pituitary diabetes insipidus
  - Primary nocturnal enuresis
  - Nocturnal polyuria

Efficacy of Desmopressin (short term)

Efficacy of Desmopressin (long term)

Safety of Desmopressin (short-term)


Mean no. of nocturnal voids (+SD) in male & female patients by treatment period. (values above bars indicate no. of patients) Lose et al. J. Urol 2004; 172:3021-5.
**Efficacy of Desmopressin (long term)**

Mean duration of first sleep period (+SD) in male & female patients by treatment period. (values above bars indicate no. of patients)


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**Safety of Desmopressin (long term)**

- Most adverse effects are mild to moderate in severity.

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**Hyponatremia**

- Reports to be around 5-14% patients.
- Risk factors:
  - Elderly
  - Concomitant cardiac diseases (IHD, AF, CHF, previous MI), renal failure, cirrhosis.
  - Low basal Na level.
  - Increased baseline 24hr urine output.
- Required regular monitoring of body weight, presence of edema and symptoms of hypoNa.
- Check electrolyte one week after starting treatment and regularly afterwards.
- Restrict water intake after evening.

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**Diuretics**

- Frusemide 20-40mg 6hr before bedtime.
- Especially good for those with fluid retention state in the daytime.
- Studies showed significant reduction in nocturnal voiding and nocturnal urine volume.

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**Imipramine & Other TCAs**

**Actions:**

1. Central and peripheral anticholinergic activity with direct inhibitory action on smooth muscle.
2. Inhibit the central re-uptake of serotonin and nor-adrenaline.
3. Inhibit peripheral catecholamine re-uptake, resulting in a sympathomimetic effect.
4. Anti-diuretic action independent of ADH.
   - Effects are reported to be due primarily to α-adrenergic receptor stimulating action in the proximal tubules, and secondarily to increased distal tubular urea and water reabsorption.
   - TCAs and anti-psychotic drugs are common causes of SIADH.

**Imipramine & Other TCAs**

- Studies showed effectiveness in the treatment of nocturnal enuresis.
- No RCT on Tx of Nocturia.
- Adverse effects include cardiovascular effects (esp. arrhythmias), drowsiness, reduction in attention span, concentration and capability for reflex movement.
Anti-muscarinic Drugs for OAB
- Commonly used drugs include:
  - Oxybutynin, Tolterodine, Solifenacin, Tropisium.
- Actions:
  1. Anti-muscarinic action to relax detrusor muscle.
  2. May also involve sensory nerve action mediated by the muscarinic receptors.
- Efficacy similar but differences in incidence of adverse effects and duration of action.

3. Pharmacologic Treatment

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