**The International Continence Society Standardisation of Terminology in Nocturia**

**Hashim Hashim, Marco Blanker, Jens Christian Djurhuus, Jane Meijlink, Vikky Morris, Peter Petros, Jian Guo Wen, Alan Wein, Marcus Drake**

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1. **INTRODUCTION**

In 2002, the International Continence Society (ICS) defined nocturia as the complaint that the individual has to wake at night one or more times to void (REF). Since that publication, several studies have been conducted looking at the epidemiology, pathophysiology and treatment of nocturia leading to a wealth of new information (REF), using a definition which was novel at that time. It has been established that people can get up at night to void to pass urine for various reasons which may or may not be pathological and as such nocturia can occur as a clinical entity in its own right for non-medical reasons such as a baby crying, or a partner snoring. These latter scenarios would be excluded as the person would have not woken up to void but had a convenience void. It may also be part of other conditions which may or may not be related to the urinary tract. Therefore patients can present and consult not only to urologists but also to other clinicians such as gynaecologists, geriatricians, neurologists, sleep experts, endocrinologists, cardiologists, immunologists, rheumatologists and general practitioners. Each specialist is likely to approach nocturia in a different way depending on the presentation. However, it is important that all health-care providers speak the same ‘language’ and refer to the same condition using specific definitions, to avoid confusion and any misunderstandings.

The ICS has therefore formed a new working group to revise and update the 2002 standardisation document on Nocturia and make new recommendations on terminology based on the published literature, since the 2002 document . This document will only deal with terminology which can then be used to further clinical practice and research and will not be addressing the epidemiology, pathophysiology or treatment of nocturia or any of its subcategories, as that is not the main aim of the Standardisation Steering Committee, is beyond the scope of this article, and is covered in several other publications (REF).

The document will address the following terms (Table 1):

1) Nocturia

2) Nocturnal polyuria (NP)

3) 24-hour polyuria

4) Nocturnal frequency

5) Nocturnal enuresis and nocturnal incontinence

**Table 1. Definitions of terms associated with nocturia**

|  |  |
| --- | --- |
| **Term** | **Definition** |
| **Nocturia** | The number of voids after falling asleep until the time the person decides to get up for the day. (this allows N=1, when someone wakes eg at 0430 but cannot get back to sleep but had expected to sleep until 0630) Report of waking up at least once to pass urine.(CHANGED) |
| **Nocturnal urine volume** | Total volume of urine produced during the night, beginning after the last void before falling asleep and including the first morning void after the individual the gets up for the day decides that they are not going to sleep anymore. (CHANGED) |
| **Rate of nocturnal urine production** | Nocturnal urine volume/time after the last void before falling asleep until the individual the gets up for the day  (NEW)Measured in ml/hr.  |
| **Nocturnal polyuria** | Excessive production of urine after the last void before falling asleep until the individual the gets up for the day during sleep. (CHANGED) |
| **Nocturnal polyuria index (NPI)** | Nocturnal urine volume/24-hour voided volume(UNCHANGED) |
| **24-hour voided volume** | Total volume of urine passed during a 24-hour period excluding the first morning void of the period (1st void is discarded and 24-hour period begins at the time of the next void and is completed by including the first void the following morning) (CHANGED) |
| **24-hour/ Polyuria** | 24-hour voided volume in excess of 40ml/kg/day. (UNCHANGED) |
| **Night** | The period of time from falling asleep to the time of intending to rise i.e. the sleep time. (CHANGED) Shift workers may have their night period during the daylight hours.  |
| **First morning void** | The first void after the intention of rising or staying up for the day. (CHANGED) |
| **enuresis** | Enuresis is reporting of intermittent incontinence that occurs during periods of sleep (CHANGED) |

1. **NOCTURIA**

In 2002, nocturia was defined as the complaint that the individual has to get up one or more times to void at night and the void has to be preceded and followed by sleep. This was the first recommendation for the definition of nocturia. It was based on assumptions of an index person weighing an average of 70 kg who sleeps 8 hours a night, with ranges generally considered to be within 2 standard deviations of this. Furthermore, that document describes night as a period of time between going to bed with the intention of sleeping and waking with the intention of rising. Only intended sleeping time is considered, not time intentionally awake in bed.

Night-time frequency was defined as the number of voids from the time an individual goes to bed with the intention of going to sleep to the time the individual wakes with the intention of rising. Twenty-four hour urine production begins after the first void produced after rising in the morning and is completed by including the first void on rising the following morning. Obviously this is a hypothetical assumption and also does not take into account the differences in gender. The definition has caused some debate, including the fact that getting up once at night to void may not be bothersome and therefore is not a “complaint”. Furthermore, it can be very difficult determining the “reason for waking”, and confirming that waking was in order to pass urine. What clinicians and researchers wanted was to define a clinical condition.

In the past years, various studies have been published on nocturia. It seems however, that only few have critically discussed the definition of nocturia. In fact, in many studies, nocturia has not been defined at all, leaving the reader unknown to what nocturnal voiding frequency is considered as nocturia. In a systematic review (REF) on the association between nocturia and nocturnal polyuria (NP), it was found that the following nocturnal voiding frequencies were used to define nocturia: ≥1 nocturnal voids (16 studies), ≥2 (34 studies), ≥3 (seven studies), and ≥4 nocturnal voids (one study). In 12 studies, nocturia remained undefined. There are no publications on the clinical prevalence/incidence of nocturia, that is, the prevalence/incidence of people presenting to a physician because of the complaint of nocturia. Most studies on patients with “clinical nocturia” (as the reason for encounter) lack information on the background population. Notably, many studies on various aspects of nocturia, had long inclusion periods, possibly reflecting a low clinical prevalence. Prevalence of nocturia in the general population is well described, for men and women of different ages, worldwide (REF). As mentioned above, this reflects nocturia as a symptom, not as a complaint presented to physicians. It is agreed that nocturia can have mixed and multiple aetiologies.

The ICS 2002 definition of nocturia did not take into account:

- people who need to void multiple times in the night after falling asleep, often several times in a row, small amounts at a time, and may not be able to get off to sleep again,

- people whose bladder does not empty fully, and who consequently need to void again soon,

- people who suffer from insomnia or difficulty in sleeping from other causes as well as their bladder.

Nonetheless, it is important to have a definition for nocturia that can be used in both clinical practice and research.

**Recommendation: The committee recommends that the definition of nocturia is changed to ‘waking up at least once to pass urine’ and ending with the intention of rising for the day.**

In other words, the committee believes that the word ‘complaint’ should not be used for the reasons mentioned above. The definition also allows the use of the word nocturia whether it is bothersome or not, can be due to several causes, or may be an entity on its own. It also means that it does not have to be followed by sleep because in some groups of patients, for example patients with bladder pain syndrome, patients may wake up to pass urine and go back to bed or stay awake and then sleep several hours later or may not go back to sleep at all. The number of times they void while still awake and trying to sleep would still be part of nocturia episodes. The nocturia episodes stop when the person has decided that they will not go back to try to sleep again and will stay awake to resume their daily activities.

The above definition would also aim to include shift workers who sleep during the day and wake up at night. It also avoids the confusion about how much time people spend sleeping and is independent of age.

It is important to emphasise that this is only a definition of nocturia and does not take into account whether this is bothersome or not, whether it is affecting quality of life or whether it needs treatment. The aim is to have a global pragmatic definition, rather than defining or suggesting a clinical pathological entity.

1. **NOCTURNAL POLYURIA**

There seem to be a number of issues that are encompassed by a definition and discussion of the term “nocturnal polyuria”. First of all, nocturnal polyuria can be defined in a general way or a specific way. According to the ICS standardization document of 2002 (Abrams, et al, Neurourol Urodyn 2002;21:167-178), describes nocturnal polyuria as an increased proportion of a 24-hour urine output occurring at night (normally during the 8 hours while the patient is in bed). In that document nocturnal polyuria is said to be offset by lower daytime production so 24-hour production remains within normal limits. Nocturnal polyuria is listed as one of the causes of nocturia. The other categories of causation of nocturia are: low nocturnal bladder capacity despite normal global bladder capacity; low global bladder capacity; and global polyuria. A mixed etiology is also possible.

The pathophysiology of nocturnal polyuria results either from increased night-time solute diuresis, reduced reabsorption of pre-water or a combination of the two. Arginine vasopressin (AVP) and atrial natriuretic peptide (ANP) are both factors. The details are beyond the scope of this discussion but, in brief, AVP is released by the posterior pituitary with a diurnal pattern. It is a potent vasoconstrictor and pressor agent through the V1 receptor but it acts primarily on V2 receptors in the collecting duct to increase permeability to water by a cyclic AMP dependent mechanism. This leads to reduced urine production. ANP is a 28 amino-acid peptide that is released by atrial myocytes in response to atrial distention and other stimuli. It binds to specific receptors and increases glomerular filtration rate leading to a natriuresis and diuresis. It also decreases renin release causing further natriuresis and diuresis.

In the ICS 2002 document, nocturnal polyuria is described in an individual with normal 24-hour urine volume as a urine output during sleep of over 20% of the total daily output in “the young” and >33% in “the elderly” with the value of “middle-age” falling somewhere between the two. Further, the nocturnal polyuria index is described as the mean measured nocturnal volume divided by the 24-hour urine volume. In individuals <25 years old this is described as 0.14 and in those over 65 years of age, 0.34.

Nocturnal polyuria exists when the 24-hour urine volume is normal, and the nocturnal polyuria index is >0.33. However, therein lies the problem: agreeing on the quantitative specifics of what constitutes nocturnal polyuria. Many iterations are offered by multiple authors, including such diverse descriptions as >6.4ml/kg, >54ml/hr, and ≥90ml/hr.

Regardless of what definition one chooses, the diagnosis of NP includes a differential diagnosis of causation encompassing congestive heart failure, diabetes mellitus, obstructive sleep apnea, peripheral edema, excessive night-time fluid intake and ‘normal’ ageing. Other factors which have been implicated in the causation of nocturnal polyuria are an abnormality in nocturnal secretion or action of arginine vasopressor (AVP) (this describes the classical nocturnal polyuria syndrome) and any edema forming state (in addition to congestive heart failure, chronic renal disease, nephrotic syndrome, hypoalbuminemia, liver failure), comorbidities such as autonomic nervous system dysfunction, Alzheimer’s disease, multisystem atrophy, stroke, and parkinsonism (REF: Aydur and Dmochowski, 2012 and Weiss, 2012 (Nocturia: Causes, Consequences and Clinical Approaches).

Most importantly is how nocturnal polyuria is defined, as this may affect how it is treated, if at all. It is therefore important for the clinician and/or researcher to define what definition they are using to diagnose nocturnal polyuria.

As things stand and based on current available evidence it is not possible to recommend using one method of calculation over another for nocturnal polyuria.

If one uses the ICS 2002 quantitative definition of nocturnal polyuria, one finds an extraordinary high prevalence in patients with nocturia (up to 83%) (Weiss et al, (J Urol 2011;180:1358-1362). Nocturnal polyuria is cited as a major contributing factor in nocturia with a prevalence of between 76% in the NOCTUPUS trials and 88% in the United States/Canada trials in patients screened in clinical trials for nocturia which provided valuable diary data. It is unfortunate that the percents were not calculated using the 90ml/hr quantitation.

van Doorn et al, (Eur Urol 2013;63:542-547) cited prevalence data in community dwelling men age 50-78 using frequency/volume charts and calculating the percent both by the ICS definition and using >90ml/hr.

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| --- | --- | --- |
| **Age** | **33% 24h Volume** | **>90ml/h** |
| 50-54 | 70.8% | 11.8% |
| 55-59 | 74.2% | 12.2% |
| 60-64 | 78.4% | 12.5% |
| 65-69 | 85.7% | 20.4% |
| 60-78 | 88.3% | 23.8% |

Hofmeester et al, (BJUI 2015;115:520-536) report 19 different ways of characterizing nocturnal polyuria. Clearly, clarification and standardization is sorely needed!

From clinical practice, we have learned that the 20% and 33% numbers do not seem to be terribly specific or accurate, unless nocturnal polyuria is in fact present in almost every patient with nocturia. However it is easy to use and calculate. Should the threshold be a higher percentage or should we simply use an absolute value? If the latter, then one will have to take into consideration the presence of 24-hour polyuria and its effect on pathophysiology. However, it may be that using a higher percentage number or using an absolute value such as 90ml/hr would better specify those patients that would be more responsive to fluid restriction and antidiuretic hormone.

Therefore new terms that can be used include:

* 24-hr urine production rate (mls/hr)
* nocturnal urine production rate (mls/hr)
* nocturnal urine production rate index.

Absolute values are yet to be defined for these terms but will be dependent on fluid input, the population defined and the gender.

To get a full appreciation of the difficulties in quantitatively defining nocturnal polyuria, one should read the section on “nocturnal polyuria in older men as defined by the Krimpen study” (Ruud Bosch), (van Doorn et al, Eur Urol 2013;63:542-547; Blanker et al, Urology 2002;60:612-616) contained in the nocturnal think tank report from the ICI-RS in 2011 (Weiss et al, Neurourol Urodyn 2012;31:330-339). This section begins by stating that the currently suggested ICS definitions of nocturnal polyuria (>20% in young adults and >33% in those over 65) were not based on normal distributions and were not properly validated. In the Krimpen study, urine production for each hour of the day was computed and urine production was assumed constant between two voidings, and hourly urine production was estimated as the volume of each micturition divided by the number of hours that passed since the previous micturition. Nocturnal urine production per hour was estimated as the mean between 1am and 6am. At baseline, a three-day frequency/volume chart was completed by 95% of the participants and the mean nocturnal urine production was 60.6ml/hr in men age 50-78 years with a standard deviation of 32.6. Linear regression analyses on nocturnal urine production was performed to identify possible determinants and the significant determinants of increased nocturnal urine production were found to be age, smoking and 24-hour polyuria. The mean nocturnal urine production in milliliters per hour for the age strata 50-54, 55-59, 60-64, 65-69 and 70-78 were found to be, in milliliters per hour, 53.4, 54.2, 58.3, 62.8, and 66.6. In men with 24-hour polyuria the mean nocturnal urine production was much higher – 101ml/hr. Based on a logistic progression analysis, a nocturnal urine production exceeding 90ml/hr was determined to be abnormal. About 1/3 of men with increased nocturnal urine production according to this cut-off value had 24-hour polyuria. Further, urine production for every hour of the day was determined and two different definitions of nocturnal polyuria were used: the current ICS definition and production of >90ml/hr. Using the ICS definition, the prevalence rises from 42% between 50-54 years to 58% between 70-78 years. The lowest prevalence was using the 90ml definition, 12.1% in men between age 50-54 to 24% in men between the ages of 70-78. Interestingly, nocturnal polyuria in women has been subject to much less investigation than in men. Nonetheless these numbers are only for men, but what about women? We have no values for women as yet!

To summarise, there are several definitions in the literature that could be used to indicate nocturnal polyuria including:

1) Nocturnal urine production of greater than 6.4ml/kg/sleep cycle (REF).

2) Rate of nocturnal urine production >90mls/hr is suggestive of nocturnal polyuria in men (about 450mls per 8 hours sleep). There are no studies to look at the rate of nocturnal urine production in women and this may well be different from that in men.

3) Nocturnal polyuria index based on nocturnal urine volume as part of total 24-hr urine volume (age dependent)

• 33% in elderly e.g. >65

• >20% in younger individuals

• 20-33% in “middle age”

4) Nocturia index

• >1: nocturia occurs because maximum voided volume is smaller than nocturnal urine volume.

• >1.5: nocturia secondary to nocturnal urine over-production in excess of maximum bladder capacity i.e. nocturnal polyuria

**Recommendations: The committee recognises the limitations and difficulties that are present in defining nocturnal polyuria. It believes that there is not enough data in the literature to make a recommendation on adopting a new definition of nocturnal polyuria. Further research is needed into this field before adopting a new definition as every definition above has limitations. In simple terms, NP is the excessive production of urine during sleep. How large is large, is yet to be defined? However, the committee believes that the way forward for new research is to have an absolute number based on rate of urine production during the night or when the patient has gone to sleep, relative to the urine production rate in 24 hours, for the various age groups and both genders. Ultimately, the definition will be used to aid treatment of a bothersome complaint and the treatment will be targeting the cause rather than the definition. It should also be easily used in research. Whichever definition is used, the health-care provider or researcher would need to specify exactly what parameter they have used to diagnose nocturnal polyuria.**

1. **GLOBAL/24-HOUR POLYURIA**

Global or 24 hour polyuria is defined as a 24-hour urine output >40ml/kg, in men and women, causing daytime urinary frequency and nocturia occasioned by a general increase in urine output, outstripping even normal bladder capacity. Volumes passed daily vary considerably, and are influenced by environmental, physiological and pathological factors, which can affect the amount of fluid loss by other means, such as perspiration, and the amount of fluid intake. (Weiss, 2012, Nocturia: Causes, Consequences and Clinical Approaches).

One confounding issue is that if one uses an amount as the indicator for nocturnal polyuria, then even with a normal distribution of day and night output, virtually all people with global polyuria will have nocturnal polyuria. If one uses a percent of total 24-hour urine output, and if the normal circadian rhythm is preserved, they will not.

1. **NIGHT-TIME FREQUENCY**

The 2002 ICS terminology document defines night-time frequency as is the number of voids recorded from the time the individual goes to bed with the intention of going to sleep, to the time the individual wakes with the intention of rising. The current definition of nocturia does not include voiding between the time of going to bed and the time of falling asleep at night and between waking up and rising in the morning i.e. nocturia is during actual sleep time. Consequently, the definition of night-time frequency is questioned due to undefined sleep time. No doubt, the linguistic ambiguity in the definition of nocturia makes mutual understanding difficult, leading to confusion. A lack of uniformity in technical terms may also cause confusion and prevent scientific progress or appropriate diagnosis and treatment.

Do we therefore need the term night-time frequency? It has been suggested by some that the term nocturia should be replaced by ‘night-time frequency’. The term ‘increased frequency’ could be used to describe the complaint that the patient is voiding more. In this way, naturally increased frequency during the day is ‘increased daytime frequency’ and during the night is ‘increased night-time frequency.’ Night-time in this context would mean the period from going to bed with the intention of sleeping until waking with the intention of rising. Night-time voiding excludes both the last void before going to bed at night and the first void in the morning after rising.

However, it has to be noted that very few epidemiological studies, if any, use the ICS definition of night-time frequency as it currently stands and the studies have looked at nocturia instead i.e. during actual sleep time. In fact it has been suggested that any voids between going to bed with the intention of sleeping and actually falling asleep, should be part of day-time frequency as the patient is technically still awake and has not fallen asleep. For example if a person goes to bed at 10pm to read a book and falls asleep at 11pm, but actually voids twice between 10pm and 11pm then these two voids should be part of daytime frequency voids as the individual has not fallen asleep yet. This would also compliment the ICS 2002 increased daytime frequency definition: number of voids recorded during waking hours and includes last void before sleep and the first void after waking in the morning. If that were to happen then this would avoid any confusion between the terms ‘night-time frequency’ and nocturia.

Therefore any number of voids occurring from the time of waking up with the intention of rising until actually falling asleep would be part of day-time frequency, and any voids occurring from actually falling asleep to waking with the intention of rising would be part of nocturia. This distinction looks strictly at the number of voids rather than volumes. It has to be remembered that if we are to look at volumes voided, then the first morning void after waking with the intention of rising up for the day would be part of the nocturnal voided volume.

**Recommendation: The committee suggests that the term night-time frequency no longer be used as it is confusing. Any voids after actually falling asleep until the intention of rising will be part of nocturia and any voids from the intention of rising up to prior to falling asleep will be part of daytime frequency.**

1. **NOCTURNAL ENURESIS**

Nocturnal enuresis has not been defined in the 2002 nocturia document. However in the 2002 ICS standardization document of lower urinary tract symptoms, enuresis was defined as any involuntary loss of urine and if it is used to denote incontinence during sleep it should always be qualified with the adjective “nocturnal”. Hence, nocturnal enuresis was defined as the complaint of loss of urine occurring during sleep. Urinary incontinence was defined as the complaint of any involuntary leakage of urine.

The International Children’s Continence Society (ICCS) have defined nocturia as the complaint that child has to wake at night to void. Nocturnal enuresis was defined as both a symptom and a condition of intermittent incontinence that occurs during periods of sleep. Previously it was wetting in discrete portions while asleep after the age of five. It is a symptom reflecting many different pathologies, previously believed to be a complete emptying of the bladder but later identified as both complete and incomplete emptying of the bladder. A general feature is that the bladder capacity of the particular individual is exceeded with the enuresis episodes. It can be provoked even in completely dry children, at least up to the age of 12 years, especially in boys by way of fluid load. Enuresis can be monosymptomatic or non-monosymptomatic. The latter is seen in individuals who also have daytime lower urinary tract symptoms. Traditionally, enuresis is divided into primary or secondary, if the individual has experienced half a year of full dryness. The latter is an arbitrary definition where the pathology seems to be identical with the primary type. The perception of enuresis pathogenesis has undergone marked changes over the past 30 years from a psychiatric/psychological background to a more somatic model where night-time urine production and bladder capacity are main components together with an arousal dysfunction that prevents the enuretic child from waking up to the signals of a full bladder. Furthermore, it has become very clear that several pathogenic mechanisms exist either alone or in combination explaining the variety of clinical subtypes with different response to treatment.

Based on the above, new definitions are needed for enuresis and its various subcategories which would need to be aligned with the ICS lower urinary tract symptoms standardization of terminology document and the neuro-urology one as well.

It can therefore be easily seen that urinary incontinence and nocturnal enuresis can easily be confused and the terms incontinence and enuresis have been used interchangeably. The distinction between nocturnal enuresis and nocturnal urinary incontinence therefore has to be made by the state of sleep. If leakage occurs when the patient is asleep then that is enuresis and it will be a subset of nocturnal urinary incontinence. Nocturnal urinary incontinence would therefore encompass several conditions including nocturnal enuresis, stress incontinence and urgency incontinence. This then assumes that both enuresis and incontinence are part of storage symptoms.It is beyond the scope of this paper to look at the pathogenesis of nocturnal enuresis.

**Recommendation: Nocturnal enuresis is leaking or passing urine while asleep. In other words it is the reporting of by the individual that they have wet themselves or the bed without knowing and have been asleep during that process.** **Obviously this definition does not take into account the aetiology.**

**Example of frequency/volume chart analysis**

|  |  |
| --- | --- |
| **Daytime** | **Night-time**  |
| Time | Voided volume (mL) | Time | Voided volume (mL) |
| Time of waking up: 07.00 | 200 | Time of falling asleep: 22.30 |  |
| 08.15 | 200 | 23.00 | 200  |
| 12.00 | 350 | 01.00 | 200 |
| 16.30 | 400 | 03.00 | 300 |
| 18.30 | 250 | 06.00 | 400 |
| 22.00 | 200 | Woke up at 08.00 next morning and voided 200 Ml |

* Maximum bladder capacity: 400 mL
* Daytime frequency: 6 times (200, 200, 350, 400, 250, 200)
* Nocturia episodes: 4 times (200, 200, 300, 400)
* 24-hour urine volume: 200+350+400+250+200+200+200+300+400+200=2700
* Nocturnal urine volume: 200+200+300+400+200=1300
* NPI: 1300/2700 = 48.1% i.e. nocturia due to nocturnal polyuria
* Ni: (200+200+300+400+200)/400 = 3.25 i.e. i.e. nocturia due to nocturnal polyuria
* NBCi: 3-(3.25-1) = 0.75 i.e. nocturia is probably *not* due to reduced bladder capacity
* 24-hr urine production rate (mls/hr) = 2700/24 = 112.5 mls/hr
* Nocturnal urine production rate (mls/hr) = 1300/9 =144 mls/hr
* Nocturnal urine production rate index = 144/112.5 = 1.28

**CONCLUSION**

The ICS 2002 Nocturia report has been very useful in highlighting the importance of standardization both in terms of research and clinical practice. The updated document has looked at the current research to help refine the currently used definitions and has highlighted the deficiencies in the literature and recommended pragmatic definitions that can be used in daily clinic practice and research. Most important of all is that health-care providers and researchers need to specify what definition they are using when treating patients or conducting research to avoid any confusion. It is also assumed that a three day frequency/volume chart is a pivotal investigation in the management of patients with nocturia. There also needs to be more epidemiological research done to help further standardize terminology for nocturia patients.

PS. I will add references later.