

NOCTURIA: A GUIDELINE

For the evaluation and management of a troublesome symptom

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NOCTURIA GUIDELINE

A Guideline for assessing and treating patients with nocturia, in a Primary Care setting in New Zealand.

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I. INTRODUCTION

i) Definitions

Nocturia has been defined by the International Continence Society (ICS) as the complaint that the individual has to wake at night, one or more times to void.¹

Nocturia can be a symptom of many different underlying conditions. The prevalence of nocturia increases with age and it is a potent factor in reducing quality of life, yet many patients and their advisors dismiss it as part of the aging process. The opportunity to assist patients is often denied as a result.

Nocturia is common. If a person has nocturia only once, and has no other symptoms, then he or she should be encouraged to accept this and not be too concerned. If the person has to go more than once, it can have a significant effect on quality of life.¹ Many get up one or more times at night, can readily go back to sleep and it causes no bother. They might consider it is normal for them. For others waking even only once is a bother as it disturbs the sleep and affects adversely well-being the next day. When it is a bother it becomes a ♦symptom♦ for which the person may seek medical help.

The ICS definition of nocturia includes the term ♦night♦, which is clearly a variable time interval. Some people sleep for a shorter time than others. Some go to bed with other things to do, or in a rest home situation because it is the policy to get the elderly into bed early for the convenience of the carers.

The length of night is probably best determined by the patient, as the *intended sleep time*, as the need to interrupt this forms the basis of the patient's complaint. It also bypasses the fact that there is a very wide variation in intended sleep time in the community.

ii) Epidemiology of Nocturia

The prevalence of nocturia in the community is high and increases with age in both sexes. There is a surprising lack of information, or uniformity in the literature about definition of the term and the number of nocturnal voidings that are used in the inclusion criteria for many of the studies.

Prevalence increases with age in both men and women. In an observational study using a definition of two or more nocturnal voids, men aged 40-49 had a prevalence rate of 16%, increasing to 55% in men over 75². Another study showed 20% of men and 21% of women aged over 40, to have nocturia.³

In a study from the Netherlands using the ICS definition, nocturia was experienced by 17% of men aged 18-34, 34% of men aged 35-54, 62% of men aged 55-74, and for men over 75 the prevalence was 80%. The figures for women similarly increased with age. Nocturia was noted by 36% of women aged 18-34, by 51% aged 35-54, by 86% aged 55-74, and by 77% in those aged over 75.⁴ In a UK study of nocturia in women, the prevalence was 16% of women over aged 19.⁵

In another UK study of 578 men, of those aged 60-69, 52% had nocturia once, while in the age group 70-85, 71% had nocturia. For nocturia twice a night or more, the prevalence was 22% and 29% for respective age groups.⁶

Despite the variations in these reports, it is clear that the prevalence is quite high.

iii) Clinical questions addressed by the Guideline Development Team

The Development Team considered several clinical questions in developing the Guideline.

1. What is bothersome nocturia?
2. What are the important treatable causes of nocturia?
3. How do sleep disorders impact on nocturia?
4. Does nocturia increase the risk of falls in the elderly?
5. How should a patient with bothersome nocturia be evaluated in a Primary Care setting?
6. What investigations should be done before treating nocturia in a primary care setting?
7. Which patients and conditions, can be treated in Primary Care, and which patients need referral?
8. Can daytime life-style changes and daytime bladder retraining, reduce nocturia?
9. When is Desmopressin effective, and safe?

II. PURPOSE OF THIS GUIDELINE

Nocturia is common, and it is the symptom, among the others of a group of lower urinary tract symptoms (LUTS) including frequency urgency and sometimes urge incontinence, that causes the most bother to the patient. The purpose of this *Guideline* is to produce an algorithm, supported by evidence, to help the

busy medical advisor or nurse practitioner in Primary Care, to determine the most likely cause, and thence to decide on the most appropriate treatment plan.

This document gives the background evidence used to develop the Guideline and the algorithm for evaluation and management of bothersome nocturia.

III. DEVELOPMENT OF THIS GUIDELINE

This NZ Guideline has been developed by an ad hoc committee of interested clinicians with backgrounds in general practice, urology, geriatrics, urotherapy and continence advice, nephrology and clinical pharmacology. Membership details are provided in Appendix 1.

The Development Team attempted to provide answers to the clinical questions posed above.

This guideline and its recommendations are concordant with the International Guideline developed by a group of international interested urologists, gynaecologists, endocrinologists, geriatricians, general practitioners, urotherapists and continence advisors, and experts in sleep disorders and their management, who participated in an International Consultation on Nocturia in London in 2002. The proceedings were formally published.⁷ A second one in Malta in 2003 revised the situation and developed an algorithm.

Definitions and terminology used are as recommended by the International Continence Society and its Standardisation Committees.

Levels of evidence for any findings have been researched and the recommendations for investigation and treatment, given a grading according to the Oxford classification. (Appendix 2)

An algorithm was developed (Appendix 3) and this has been based on information included in the text of this document.

The Guideline will be further discussed with Professional colleagues, by patient consumer groups, and the relevant parent bodies of the medical disciplines involved before being modified.

Revision of these Guidelines

This Guideline will be presented on the website of the NZ Continence Association by the end of 2005. It is anticipated that with usage and with experience in practice, and with steadily increasing knowledge, there will be a need for regular revision of this guideline. Comments are welcomed by the Committee. The target date for revision will be 2008.

Financial disclosure

Ferring (NZ) assisted us with an unconditional grant towards the costs of our meetings, and in researching documents from the literature. The committee had complete editorial independence. No conflicts of interest were declared by the Development Team members.

IV. GUIDELINE INFORMATION

Summary

Some patients with nocturia can go straight back to sleep afterwards, and are not unduly bothered by the symptom. Most are not unduly bothered until the need to get up reaches twice or more times. Some patients have an underlying sleep disorder which is the reason for the nocturia. Patients may present with other lower urinary tract symptoms as well as the nocturia, and require further evaluation.

Nocturia has many causes and the purpose of this Guideline is to assist Primary Care practitioners and nurse specialists, and urologists and other medical advisors, in the identification of treatable causes, and their appropriate management.

Simple changes to the intake of fluids, the timing type and volume, may reduce or eliminate the nocturia among those who haven't worked that out for themselves. About half of the patients with nocturia have normal bladder function and normal urine outputs,⁸ suggesting that simple measures should be helpful in this group.

The initial assessment by history, past medical history and examination will allow a preliminary diagnosis in many cases. This should be followed by urinalysis and ultrasound assessment of the post-void residual urine volume, where available. This information should enable one to detect and diagnose conditions like haematuria, sleep disorders including sleep apnoea, inappropriate fluid intake at night, congestive heart failure, chronic obstructive airways disease, and gynaecological prolapse in women, and for these, specialist advice may be indicated. Those men who have symptoms of voiding dysfunction might benefit from alpha adrenergic blocking drugs, and if this should fail then referral to a urologist needs to be considered. For those unresponsive to these measures, and for those in whom a diagnosis has not yet been reached, then further assessment should be considered.

For this a bladder diary should be used to look at intake and output of fluids over a 24 hour period. If practicable this should be continued for 3 days. This will indicate firstly if the functional bladder capacity is reduced, and secondly if the patient has polyuria, either nocturnal only, or throughout the day and night (global polyuria).

There are multiple causes for reduce bladder capacity which may be functional, or mechanical. Mechanical causes include bladder wall fibrosis or masses pressing on the bladder. Functional causes are often due to detrusor overactivity, increased sensitivity or bladder pains. Simple measures include life-style advice, bladder retraining and pelvic floor muscle exercises sometimes supplemented with anticholinergic drugs are often helpful. Non-responders should be referred for specialist advice. Those identified as having the chronic pelvic pain syndrome, interstitial cystitis, or chronic abacterial prostatitis, can be managed initially by the primary care practitioner, but often require specialist referral. Global polyuria has been defined as 24 hour urine output exceeding 40mls/kg.¹ It can be due to either water or solute diuresis. Water diuresis is usually due to inappropriate antidiuretic hormone (ADH) secretion, or polydipsia. Most require specialist referral. Solute diuresis is usually due to the osmotic effects of excessive glucose, sodium, albumen, or urea in the urine. Urine osmolality is low in cases of water diuresis, and high in those with solute diuresis. Life-style advice, treatment of diabetes mellitus or of renal impairment if present, may help. Specialist referral may be required for many of these clinical problems and for those who do not respond to initial advice.

Nocturnal polyuria is defined where the nocturnal urine volume exceeds 33% of the 24 hour volume.¹

A lower nocturnal urine volume of around 22% of the 24 hour total is sometime observed in younger patients. For patients with nocturnal polyuria who do not respond to life-style advice, a trial of diuretic medication in the afternoons to reduce any postural oedema may be helpful. Treatment with an analogue of ADH, desmopressin (Desamino, D-Arginine VasoPressin or DDAVP), can be considered with accepted cautions, for non-responders in this group.

1. INTRODUCTION

The purpose of this guideline is to propose a framework algorithm based on the International Algorithm for the assessment and management of nocturia in adults. It should be of help to primary care physicians and practice nurse specialists, to urologists and specialists in other disciplines who manage such patients in community or hospital settings.

Nocturia can occur if sleep is interrupted because of sleep disorders, due to psychological, behavioural or environmental issues. But it is axiomatic that a person will need to rise at night to void if the nocturnal

urine volume produced exceeds the maximum functional bladder capacity as measured in the daytime by using a bladder diary. There may be combinations of these causes and nocturia is often multifactorial.

Attempts to reach a diagnosis and to plan treatment, should include an initial evaluation process, based on the clinical presentation, the past medical history, and drug therapy, and the clinical examination. (Step 1). Preliminary lab tests include urinary and blood tests. (Step 2). These initial steps 1, and 2, are discussed below.

At the end of this process, a diagnosis and management plan can be achieved in many cases, or the indications for referral for specialist opinion, can be identified. If not, then Step 3 in the process involves recording a bladder diary to define whether the person has polyuria, or a reduced functional bladder capacity.

2. QUALITY OF LIFE (QOL) ISSUES

It is clear that nocturia can have a very significant impact on the patient's quality of life.^{9,10} A measure of the impact of the nocturia on quality of life should be made. The International Prostate Symptom Score (IPSS) can be used in both men and women for this purpose. After the planned intervention the QOL test can be repeated for comparison. It should take into account the patients own goals and expectations in seeking assessment and treatment.

3. FINDING A CAUSE

3.1 STEP I: CLINICAL EVALUATION FOR RISK FACTORS

From a focussed history and clinical examination, from the past medical and surgical history, and a record of the drug treatments, a diagnosis can often be identified. This can lead to simple life-style or other recommendations to the patient. For others, the risk factors for nocturia can often be identified and these need to be sought and treated if possible.

a) Risk Factors Identified from the history: Step 1.

i). Fear of Cancer

Prostate cancer is very common among older men, and is often on the patient's mind when seeking medical advice, even if not overtly stated at the beginning of the interview. Prostate cancer develops in the posterior margins of the prostate in most cases, and does not produce any urinary symptoms or urethral compression until it has reached a late stage. Early cancer of the prostate is relatively symptom free. With a normal feeling prostate on digital rectal examination, and a normal Prostate Specific Antigen (PSA) blood test, a man's chances of having prostate cancer are minimal. With re-assurance about this, many men are happy to continue as they are without further assessment or treatment for the nocturia.

A urological opinion should be sought, if the prostate feels abnormal on digital rectal examination, if the PSA is persistently above normal, if there is a strong family history of prostate cancer, or if the patient is concerned about cancer.

ii). Ageing

Nocturia increases with ageing and is multifactorial in origin. Some causes are related to ageing and others to the increase in other bladder related co-morbidities which are also commoner in the older person.

In a study of the causes of nocturia in 129 elderly women and 65 men based on history, examination, bladder diary, post-void residual urine, and urodynamics, 57% had nocturnal detrusor overactivity, 7% had nocturnal polyuria, and 36% had a combination of nocturnal polyuria with detrusor overactivity. Nocturnal polyuria is a significant component of nocturia in 43% of patients. As most of these will also have detrusor overactivity, therapy should be directed at both components.¹¹

It should be noted however that one recent study from Sweden, showed no correlation between the number of nocturnal voids and a known and treated background of hypertension, angina, congestive heart failure or diabetes.¹²

Some other causes related to ageing, are listed below.

i) ADH production

A circadian rhythm of ADH production is established in most children between the ages of 2-5 years. Delay in its development is associated with persistence of nocturnal enuresis. In adults over the age of 60, loss of this diurnal rhythm is one cause of nocturnal polyuria.¹³ Plasma ADH and angiotensin levels were lower at night in a group of 17 elderly patients with nocturnal polyuria.¹⁴ Of the 17 patients, 11 had nocturnal polyuria the others were normal. The studies were poorly designed cohort studies.

Level of evidence: Level 3

ii) Renal water loss

With ageing there is a reduction in concentrating ability of the kidney.¹³ In a cross-sectional study of patients with a 24 hour water deprivation test, the maximum urinary specific gravity attainable by young subjects was around 1030, but by aged 89 this had reduced to 1023.¹⁴ This appears related to reduced tubular response to ADH (a type of partial nephrogenic diabetes insipidus), or to age related effect on the efficiency of the renal collecting tubules.

iii) Sodium losing nephropathy

This can occur in some renal disorders and result in an increased osmotic load hence a solute diuresis.

iv) Renin-angiotensin-aldosterone

Posture change from supine to standing in the elderly produces less of a response in the renin production, and hence less active angiotensin and aldosterone.¹⁴

v) Atrial Natriuretic Hormone (ANH)

Serum ANH increases in the elderly causing further sodium loss and an osmotic diuresis. Minimal increases in ANH can also inhibit angiotensin II induced aldosterone secretion and again tend to lose sodium by this second mechanism.

iii). Lower urinary tract symptoms of bladder storage, or voiding dysfunction (LUTS).

It is often helpful to ask the patient to complete a validated symptoms score assessment like the International Prostate Symptom Score IPSS. This is valid for both men and women.

◆ *Bladder outlet obstruction* can be accompanied by increased frequency and nocturia, partly because of detrusor over-activity due to the obstruction and partly because of ageing. Voiding symptoms of delay, poor flow and a sensation of incomplete emptying are often present, but nocturia is the commonest single reason why a male seeks attention for these symptoms. Obstruction is defined in urodynamic terms as a slow flow rate, with high voiding pressures, and an area of urethral narrowing seen on voiding Xray studies. Surgical ablation or pharmacological relaxation of this area, should allow

the other parameters to regress to normal. Not all those with these symptoms and a slow urinary flow rate are obstructed. Some will have poor detrusor contractility which is very common in the elderly.¹⁵ Tests can include a voiding flow rate measurement, and post-void residual urine test most easily assessed with ultrasound where available.

◆ *Chronic retention of urine:* In this condition there is a very large residual urine (>300 mls), so that frequency and nocturia result from the reduced functional bladder capacity. The person is voiding only a small amount each time and it takes only a short time before the bladder is again full. The bladder usually remains palpable after voiding.

◆ *Neurological disorders:* A second cause is the overactive detrusor secondary to neurological disease. It may be accompanied by urgency and urge incontinence. Symptoms of clumsiness, or weakness, unsteady gait or visual disturbances might be subtle, and these should be actively sought in history taking. It is common in patients with multiple sclerosis and in Multi-system atrophy (MSA), and in some with Parkinson's disease.¹⁶ While many patients with multiple sclerosis also develop urinary symptoms, in about 2% of patients, urinary symptoms are the first sign of a neurological problem, and the neurological symptoms develop only subsequently.

Some patients with Multiple Sclerosis or Parkinson's Disease, can benefit from using Desmopressin, in terms of reduced nocturia.¹⁷

In patients who use wheel chairs, recumbency corrects postural hypotension and encourages the reabsorption of lower limb postural oedema accumulated during the day. This increases the urine volume and appears to be the main cause of nocturnal polyuria in these patients. Loss of circadian rhythm of ADH production has been identified in some paraplegic and tetraplegic patients. An observational study showed that this nocturnal polyuria responded to desmopressin administration.¹⁸

◆ *Symptoms of the overactive bladder (OAB).* These include increased frequency of voiding and nocturia, and urgency with or without urge incontinence. Urodynamic testing may reveal idiopathic detrusor over-activity.

There is Level 3 evidence that delayed resolution of persistent primary enuresis in childhood may be important to note, as overactive detrusor dysfunction is more likely in later life, and with an earlier age of onset, compared to those who became dry within the usual age range.^{19,20} Most children with enuresis and overactive detrusor dysfunction do improve with maturity, although a small number (13%) go on into adult life with persisting symptoms.²¹

Good results can be achieved in some men and women by bladder retraining supplemented with anticholinergic drugs and for women with urgency and urge incontinence, frequency and nocturia. Level of evidence: 1-2²²

For men, with symptoms of OAB, there have been few studies. Bladder retraining and pelvic floor muscle exercises can help post-prostatectomy incontinence, but there is no evidence that it helps for nocturia.²³

◆ *Detrusor Overactivity (Hyper-reflexia) and Impaired Contractility (DHIC)*¹⁵ In this condition which is common in the ageing bladder, there is a combination of symptoms of OAB and of voiding difficulties. Urodynamic studies indicate the presence of detrusor overactivity and impaired contractility. Significantly increased post-void residual urine is often present.

◆ *Burning and suprapubic pain* that might indicate inflammation in the bladder. Possible causes are listed.

UTI

Chronic inflammation

TB

Bladder tumours, stones

Radiotherapy. Radiation cystitis and ensuing fibrosis can

continue to occur indolently over time and produce symptoms

sometimes years after the treatment was given.

Schistosomiasis, occasionally seen in traveller returning to NZ after visits to endemic areas in Africa, Middle East and Asia

Chronic pelvic pain syndromes which include:

interstitial cystitis

chronic prostatitis

endometriosis

Contact inflammation

colonic diverticulitis

endometriosis

iv). Haematuria

This might indicate a urological tumour, stones or infection, and always needs further investigation, which might include urinary microscopy and culture, urine cytology, imaging of the upper urinary tract (IVU or CT), and a cystoscopy. Patients with macroscopic haematuria or persistent microscopic haematuria need urgent urological referral.

A small number will have associated significant proteinuria due to renal parenchymal disease, and require nephrological review.

v). Obstructive airways diseases

Respiratory disorders associated with increased airways resistance like sleep apnoea, are associated with increased renal sodium and water excretion mediated by plasma Atrial Natriuretic Peptide (ANP). This has been shown to be due to increased right atrial pressure resulting from hypoxia-induced pulmonary vasoconstriction.^{24,25}

vi). Pregnancy.

Nocturia is experienced by the majority of women during pregnancy.^{26,27} It seems more common in the first and third trimesters for reasons which are not entirely clear. Increased fluid intake and hence of urine output, pressure of the gravid uterus on the bladder, and hormonal effects may contribute.²⁷ Studies looking at this have been cross-sectional rather than longitudinal, and changes observed could be due to individual variations.

vii). Menopausal status

There is evidence that increased frequency, nocturia and urgency can be associated with post-menopausal atrophic changes in the lower urinary tract. Replacement with oestrogen/progesterone can relieve these symptoms in some patients. However in a well conducted double blind placebo controlled study of oestrogen for the urge syndrome in post-menopausal women, no significant benefit was noted and there were several who developed unwanted side-effects, particularly of menorrhagia.²⁸

Further, caution is required in prescribing hormone replacement therapy as the long-term use of oestrogen containing compounds, is associated with an increased risk of breast cancer.

The International Consultation on Incontinence²⁹ concluded that:

The disparity of results suggests a need for further studies on the effect of hormone replacement therapy for the treatment of nocturia in older women.

(Grade of recommendation is C)

viii). Recurrent UTIs

Urinary tract infections will produce episodic nocturia in association with the daytime increased frequency, and is usually associated with burning on voiding, and suprapubic pains. Between bouts these symptoms should return to normal.

Bacteriuria is common in the elderly, up to around 30% will have asymptomatic bacteriuria and urine culture is only occasionally positive. Of course if a patient is symptomatic, then culture should be done to define any infection, and then appropriate treatment is instituted.

Urinary tract TB is always secondary to primary TB of the lung, oropharynx or ileum. Blood spread takes it to the kidneys and then if the bladder is involved, this can lead to chronic inflammation and fibrosis of the bladder wall and hence reduced bladder capacity as the cause of any nocturia.

ix). Symptoms suggesting CHF and peripheral oedema

Extravascular water accumulated in the lower limbs while seated or standing is then reabsorbed and excreted at night, and is responsible for nocturnal polyuria and hence for nocturia in some.

x). Pelvic pathology

Pelvic organ prolapse can be asymptomatic but sometimes causes a dragging discomfort in the pelvis or perineum, and urinary symptoms of frequency and urgency and nocturia, and dyspareunia in some.

Observational studies indicate that repairing the prolapse can reverse these symptoms in some. Of 24 women with pre-op urgency only three had this as a problem persisting after correction of the prolapse.³⁰ Similar figures were shown in another observational³¹, where 83 Of 110 women with prolapse had frequency and urgency. After suspension, the number with frequency, nocturia and urgency fell from 83 to 17, representing a 76% improvement. Even with the symptom of urge incontinence and prolapse, successful repair resolved the co-existent urge incontinence in 24 of 38 women (63%).^{31,32}

Pelvic masses, and tumours in adjacent organs, can cause increased urinary frequency.

xi). Renal impairment: Chronic renal disease, especially nephrotic syndrome

Nephrotic syndrome is accompanied by proteinuria and this causes an osmotic diuresis. Salt-losing nephropathy can also result in a solute diuresis. Obstruction causing hydronephrosis can result in renal collecting tubule dysfunction and impaired water and solute reabsorption. It is likely this would only become apparent if the opposite kidney were poorly functioning or absent.

xii). Sleep disorders

Sleep disorders can cause nocturia, and appropriate identification and diagnosis of sleep disorders may prevent people with nocturia receiving inappropriate urological advice or treatment (eg prostatic surgery).

Sleep disruption can be caused by anxiety, sleep-associated breathing disorders (eg obstructive sleep apnoea), insomnia, anxiety, depression, alcohol use, drugs related to sleep, pain, and neurological disorders, but also increases with ageing, and of course with nocturia for other reasons.³³ Equally the nocturia itself disrupts sleep.

There is sufficient evidence to support seeking a history of sleep disorders and snoring habits when assessing nocturia. The prevalence of obstructive sleep apnoea is around 2% of women and 4% of men.³⁴

Sleep EEG patterns are variable but according to Jennum³⁵, the first third of sleep is characterised by non rapid eye movement NREM sleep at deepest stages of 3 or 4, sometimes called slow wave sleep

(SWS). Lighter sleep NRM2 and rapid eye movement REM sleep characterise the later part of sleeping time. Sleep length, REM and SWS diminish with age.

Sleep fragmentation and disruption cause daytime tiredness, mood changes, and cognitive dysfunction with poor concentration and performance.³⁶ An observational study has shown some evidence that nocturia causing loss of sleep increases the risk of falls in the elderly.³⁷ Falling can lead to fractures including hip fractures, which have serious consequences in the elderly. They estimated that the risk of falling increase from 10% to 21% if nocturia occurs twice or more.

The use of psychoactive drugs such as hypno-sedatives and tricyclic antidepressants has been considered³⁸, however particularly in older adults these agents have been associated with an increased risk of falls.³⁹ One randomised controlled trial has found the withdrawal of psychoactive medication increased the risk of falls.⁴⁰

xiii). Malignancy

Malignancy may cause bone resorption, and the resulting hypercalciuria can cause an osmotic solute diuresis.

xiv). Drugs

Diuretics, especially if taken in the evening

Fluids, especially tea, cocoa, coffee, chocolate and alcohol close to retiring time.

Drug toxicities

Lithium, can cause diuresis by a toxic effect on the renal tubules

Theophylline causes a diuresis

Phenytoin

Excessive Vitamin D. Pharmacological preparations containing Vit D (eg cholecalciferol Calcitrol) can lead to hypercalciuria and consequent diuresis.

Calcium channel blockers

b) Identifying risk factors from Clinical Examination

The clinical examination is important and should include:

i) Examination to exclude peripheral oedema or any evidence of heart failure

ii) Abdominal exam to exclude a distended bladder, or other abdominal or pelvic mass.

Abdominal ultrasound can often confirm the nature of the mass. If not clear then other imaging techniques might be needed.

iii) Focussed neurological examination where appropriate.

This should be done if there are any neurological symptoms, but examination of the plantar reflexes to exclude an upper motor neurone disorder should be included routinely.

iv) Pelvic exam should focus on the following:

While it is recognised that not all GP's would feel competent to assess accurately the degree of prolapse, present, its presence should be noted for subsequent referral to a gynaecologist or urologist, if needed. The following should be noted:

◆ inflammatory disorders Vulvitis, Bartholin's abscess, Urethral caruncle or inflamed diverticulum

◆ post-menopausal atrophic changes:

◆ pelvic organ prolapse

◆ Digital rectal examination in the male: The prostate should feel

rubbery and smooth, non-tender and is usually symmetrical. Abnormalities should alert the primary care practitioner to the possibility of tumour, or inflammation.

3.2 STEP 2: SIMPLE LAB TESTS

i) Urinalysis

This should be done to seek any evidence of white blood cells, red cells, bacteria and casts. If any of these are positive then urine culture should be obtained to determine the presence of UTI. If present in a patient with symptoms, it should be treated appropriately.

However in the elderly, it should be noted that *asymptomatic* bacteriuria is so common that it does not indicate that a full urine culture should be undertaken. About one third of women over 80 have positive dipstick test and asymptomatic bacteriuria. These findings are not necessarily an indication that treatment is needed.

As indicated the presence of microscopic haematuria demands a full urological assessment, as malignancy needs to be excluded. Haematuria may also indicate the presence of a possible nephrological cause, and this should be sought.

ii) Blood tests

Blood glucose, serum electrolytes, creatinine, and calcium levels should be checked.

To screen for the presence of glucosuria, the dipstick is good, although to detect the presence of diabetes, a fasting blood glucose level should be done.

Any identifiable cause should be treated as appropriate before proceeding with further evaluation. If such treatment is not successful then further testing is indicated.

3.3 STEP 3: BLADDER DIARY

The ICS Standardisation Committee recognises that simple life-style measures and advice on fluids and volume of intake and timing may reduce or eliminate the need to get up to void, among those who have not yet worked that out for themselves. Making life-style changes like reducing alcohol and coffee and other fluids near bedtime has been shown to reduce the nocturia. It has been estimated that about half of patients with nocturia have normal bladder function and normal urine production.⁸ In 24 hours the glomeruli filter approximately 180 litres of fluid. Of this 90% is reabsorbed in the proximal tubule and loop of Henle, while 10% goes on to the distal tubule and collecting ducts where sodium and water reabsorption is finely tuned under the influence of aldosterone and ADH respectively. The role of renal aquaporins has been overviewed by Nielsen⁴¹. The resulting final urine volume produced varies from 1-2 mls/minute under normal circumstances.

In healthy young adults the urine production at night is less than half that during the day. This is in part due to the decrease in the excretion of solutes like sodium, urea relating to eating, and in part due to the action of ADH.^{13,42,43} Elderly nocturics have a higher nocturnal urinary output and a lower volume per void compared to non-nocturic elderly patients.⁴³

Should the previously discussed measures in Steps 1 and 2, fail to produce a diagnosis or the desired response, then it is worth going on to further testing by asking the patient to record the time and volume of all urine passed during the full 24 hours. Any incontinence episodes should also be recorded. An example of such a bladder diary is in Appendix 3. It is preferable to keep this diary for 3 consecutive days, to overcome daily variations. As a result of the bladder diary, it should be possible to further categorise the problem into one of the following types:

1. Polyuria: Global
2. Polyuria: Nocturnal

3. Reduced functional bladder capacity.

Polyuria refers to excessive urine production. It may be global and occur throughout the whole 24 hours, or may be limited to night-time, as nocturnal polyuria.

1. Polyuria: Global

This is defined arbitrarily as a 24 hour output of more than 2.8 litres per day. Another definition is of an output exceeding 40mls/Kg/day. This will be detected by the 3 day bladder diary.⁴²

Global polyuria can be caused by a water or salt diuresis, which can secondarily increase the thirst and hence the water intake. It can also be caused by excessive thirst and drinking (dipsogenic) which is usually psychogenic or behavioural.

i) Water diuresis

The best way to distinguish between water and solute diuresis is the urinary osmolality, which will be >1010 in solute diuresis and <1010 in water diuresis.

a) Primary Diabetes Insipidus

The control of water balance is via osmoreceptors in the hypothalamus. In states of dehydration and increased osmotic pressure in the blood, there is an increased secretion of anti-diuretic hormone (ADH), which acts on the renal collecting tubules to increase water reabsorption. There is a normal diurnal rhythm of ADH secretion which means that less urine is produced at night than in the day. Pituitary diabetes insipidus is due to hypophyseal deficiency and occurs when the secretion of ADH is abnormally low.

Loss of this circadian rhythm of ADH production with an increase in nocturnal urine production has been identified among some patients with spinal cord injuries,¹⁸ and this responds to Desmopressin. Clearly there are other causes in paralysed patients including daytime pooling of fluid in the lower extremities, which is then mobilised when they are recumbent. Hypercalciuria from mobilisation of calcium from the bones secondary to the paralysis is another factor.

It responds to administration of Desmopressin, and modest fluid restriction.

b) Nephrogenic Diabetes Insipidus

This can result if the renal collecting tubule becomes insensitive to the circulating ADH and is probably mediated through abnormalities of the recently described Aquaporin channels. Prescribing Desmopressin produces no benefit. It can also occur in patients with bilateral hydronephrosis, in which the renal collecting tubules are compressed and become atrophic even before any effect has occurred on glomerular function. Water reabsorption and solute excretion may be impaired.

c) Dipsogenic Diabetes Insipidus

This is caused by excessive thirst which may be psychogenic or behavioural, and the large urine output is a physiological response to the huge water intake. Prescribing Desmopressin is dangerous in this condition as the patient will keep on drinking and the antidiuretic effect prevents the elimination of the excess water that is needed. Water intoxication may follow.

Treatment usually requires psychiatric and endocrinology expertise.

ii) Solute, or osmotic diuresis

In the normal person, nocturnal urine volume is regulated partly by solute excretion of sodium, potassium and urea, which are rapidly eliminated after meals and hence less at night, and partly due to circadian levels of ADH, which are higher at night.

Abnormalities in solute excretion can occur; examples are:

- ◆ *Glucose* Diabetes mellitus
- ◆ *Albumen* Nephrotic syndrome
- ◆ *Calcium* Hypercalciuria. The two most common causes are primary hyper-parathyroidism affecting 1% of adults, and malignancy. While calcitriol; and other drug related causes of hypercalcaemia do occur, they are relatively uncommon, albeit eminently treatable. Excessive Vitamin D and sarcoidosis are other causes.
- ◆ *Sodium* Salt losing states eg. Nephropathy.
Sodium excretion is under the control of aldosterone which increases the reabsorption of sodium. Hypoaldosteronism (Addison's disease) results in solute diuresis. Aldosterone levels are regulated by the renin-angiotensin-aldosterone system, which is responsive to changes in the blood pressure.

The associated water loss tends to produce dehydration, and thirst to correct it. This may need to be quantified in a 24 hour output study, as well as measuring these substances in the blood.

iii) Psychogenic polydipsia

Most of these cases will require referral to an endocrinologist and a psychiatrist, for further advice.

2. Nocturnal Polyuria

Elderly nocturics have a higher nocturnal urine production and a lower volume per void than non-nocturics.⁴³ However there are some authors who suggest this is due to affects of ageing decreasing the concentrating abilities of the renal tubules rather than secondary to ADH changes.

Criteria for investigation of nocturnal polyuria:

i) Absolute criteria

There have been several definitions of nocturnal polyuria, but no widespread agreement. Measuring the volume of output overnight, means excluding the voiding volume immediately before retiring but including the volume of the first void in the morning as this volume has been produced during the night.

There is some disagreement in the literature on definitions. One definition of nocturnal polyuria included a night-time output exceeding 0.9 mls/minute.^{42,44} This study looked at 95 elderly patients with and without nocturia. Night was defined as time spent in bed with the intention of sleeping, as recommended by the International Continence Society

Another definition included an adjustment for body weight. One group suggested a definition of nocturnal polyuria as >10mls/kg of urine produced during the night.⁴⁵ This would mean a rather large volume > 800 mls, compared to around 450 mls by the former definition of > 0.9 mls/minute.

ii) Relative criteria

Some have divided the day into one 16 hour period and one 8-hour period: (0600-2200, and 2200-0600). The ICS definition suggests that the nocturnal volume should be approximately 22% of the total 24 hour output in younger patients, but this should be less than 33% in older subjects.¹ The relative definition is appropriate only if the 24 hour volume is within normal limits.⁴⁴ The authors also point out that there is an overlap between nocturics and non-nocturics using these parameters.

3. Reduced functional bladder capacity

This refers to patients who have a reduced bladder capacity (FBC), for a variety of possible reasons as discussed. There is a range in FBC in normal people and this reduces with age. 300-450 mls would be in the normal range, with figures slightly higher for women than men. Essentially, this is nocturia occurring without any polyuria. It may also be multi-factorial.

Causes:

i) Detrusor overactivity

This refers to the presence at the time of cystometry, of uninhibited detrusor contractions occurring during bladder filling, or provoked by posture change, or coughing. It is seen in the following contexts, and is often responsible for the symptoms of an overactive bladder (OAB) frequency, nocturia, urgency with or without urge incontinence.

Bladder outlet obstruction

Idiopathic

Neuropathic

Ageing, when it is often associated with impaired detrusor contractility (DHIC) syndrome.¹⁵

At times it can be difficult to differentiate nocturnal polyuria from the role of the overactive bladder in men with nocturia. The distinction can be made by a timed volume analysis of the 24 hour voiding diary.⁴⁶

ii) Bladder inflammation+/- fibrosis

In these conditions the bladder wall is often rigid due to inflammation, fibrosis, or even tumour, s discussed above under risk factors for nocturia.

Stones, Tumours

Previous radiotherapy

Chronic inflammation, eg TB, Schistosomiasis

Chronic Pelvic Pain Syndromes

iii) Pelvic pathology

Masses can press on the bladder so that the tension in the wall rises earlier in filling giving rise to the sensation of ♦fullness♦, and resulting in increased frequency

Each of these categories may respond to specific therapy where appropriate.

4. MANAGEMENT OF NOCTURIA

Management of nocturia depends on a diagnosis and this can be reached in many cases, by following the steps outlined in the guideline. Management relies on full discussion of the patient♦s expectations, on expert advice and on common sense. In addition to the preliminary management of the condition identified, simple life-style advice might be all that is required.

If bladder outlet obstruction is diagnosed in men with LUTS and a negative PSA, a trial of an alpha-adrenoreceptor blocking agent may be helpful. For non-responders, referral to a urologist is indicated full assessment including a flow rate measurement, as he might be a candidate for a TURP.

Defining obstruction requires the presence of a low flow rate and voiding at a high pressure. These patients do better after prostatectomy than those in whom the slow flow is secondary to poor detrusor contractility. Relieving the obstruction either by alpha-adrenergic blocking drugs or by prostatectomy, causes a reduction of the nocturnal frequency in around 70% of men.⁴⁷

1. To reduce nocturnal polyuria

◆ Fluid restriction in type and volume near retiring would make sense. No studies could be identified that considered the effectiveness of conservative therapies for nocturia alone, in older people. There is some evidence that limiting of night time fluid intake, tea and coffee, and alcohol may help.²⁹ The recommendations of the International Consultation on Incontinence²⁹ were that:

◆ *Conservative management of nocturia, whilst lacking hard data appear nonetheless to be effective or helpful to many patients.* ◆

Grade of Recommendation D

◆ Medical therapy of any heart failure should be optimised.

◆ Compression therapy to prevent third spacing of fluid in the legs, and elevation of the legs in the afternoon to encourage reabsorption of postural induced clinical or sub-clinical oedema has been shown to be effective.²⁹

Level of evidence is 4

◆ Diuretics in the afternoon, about 6 hours before retiring might enable excess body water to be eliminated before the person retires.^{48, 49}

The International Consultation on Incontinence²⁹ recommended that:

◆ *Use of loop diuretics given in the afternoon to get rid of any postural oedema should be considered for further therapeutic trial since it is a simple and effective treatment in some patients provided they are screened and monitored for postural hypotension and electrolyte disturbances.*

Grade of recommendation: B

◆ Desmopressin

Desmopressin is an analogue of vasopressin with effects like anti-diuretic hormone (ADH) but without any vasopressor effects. Its use has been recommended for persistent primary enuresis in children, and for healthy younger adults with nocturnal polyuria, where no treatable cause is found.

Efficacy

Antidiuretics given at night to reduce nocturnal urine production have proved useful.

In a placebo controlled RCT of desmopressin in 151 men over 15 years of age with troublesome nocturia, and a nocturnal urine volume exceeding the functional bladder capacity, 34% of the men had fewer than half the number of nocturnal voids than the placebo group which had 3 % reduction. Significant reductions were noted in nocturnal urine volume and duration of the first sleep period before having to get up.⁵⁰

Another carefully conducted double blind RCT in 20 elderly men with known nocturnal polyuria, showed a significant reduction in nocturnal voiding frequency and nocturnal urine production, but only when the 40 microgram dose was used, not at a dose of 20 micrograms.⁵¹ There was also a significant reduction in the mean serum osmolality. Its use in the elderly requires specially caution and monitoring by body weight and serum sodium. The marketers of DDAVP do not recommend its use in those over 65.

Level of Evidence 1

Exclusions and cautions

Desmopressin should not be used in the following circumstances:

◆ Age >65years. Older persons should be excluded because of the greater risks associated with hyponatraemia. This is unfortunate as many of the patients with troublesome nocturia, are in the older age group.⁵²

◆ History of known hyponatraemia, which can occur at any age. Symptoms suggesting the possibility of hyponatraemia include headaches, nausea, vomiting, fatigue, dizziness, weight gain, and ataxia.

◆ Diuretic therapy: caution required.

◆ Renal or hepatic failure. Caution required as they can cause a significant increase in the half life of Desmopressin.

◆ Psychogenic polydipsia Desmopressin should not be used as it dangerous and can cause water intoxication.

◆ Drug interactions:

Its use should be avoided where possible in those on NSAIDs, certain antidepressants, like tricyclics, serotonin uptake inhibitors, chlorpromazine, and carbamazepine, as they can cause fluid retention.

Safety

Adverse events were seen in 15 (17%) of the desmopressin treated group, and in 16(25%) of the placebo group. Most were mild.⁵⁰

Hyponatraemia (Na<130mmol/l) was seen in 10 (4%) during the dose titration part of this study. It is recommended that the serum sodium be measured before considering treatment and repeated 3 days after starting therapy and again after any change in the dose.⁵⁰ In a systematic review and meta-analysis of cohort studies and RCTs 7 studies indicated a 7.6% risk of hyponatraemia and again emphasising caution in the elderly.⁵² A few reports have been made of patients who become hyponatraemic after the longer term use of Desmopressin. Care is required, particularly in the elderly. Its use is not recommended in those over 65.

Recommendations

The recommendations of the ICI were

Until further information is available use of Desmopressin should not be a routine treatment, although it may have beneficial effects, but only in healthy older adults.

(Grade of recommendation B).

Close monitoring for side-effects is important, especially of serum sodium and fluid balance status. There is no data to support its use in frail older patients.²⁹

2. Sleep enhancement

◆ Avoidance of stimulants like coffee, alcohol

◆ Manage anxiety

Should psychotropic drugs be considered, there is anecdotal evidence suggesting that they might work for some³⁸, but there have been no randomised controlled trials to investigate this.

Some psychotropic drugs like the tricyclics have an additional anticholinergic effect. However, psychotropic drugs have been linked to with falls in the elderly.³⁹ One other study showed withdrawal of psychoactive medication to be associated with a reduction in the risk of falls in the elderly.⁴⁰

Recommendation: *Sedatives should not be recommended in the elderly because of the increased risk of falls*³⁹.

◆ Treat sleep apnoea. This may require a sleep laboratory and the use of controlled positive airways pressure (CPAP). This was shown to be effective in some cases.⁵³
Level of evidence 3

3. To control detrusor overactivity

i) Bladder retraining.

Several studies have attested to the reduction in nocturic episodes for patients on bladder retraining programs supplemented at times with anticholinergic drugs.^{54, 55}

Level of Evidence 4.

ii) Antimuscarinic drugs:

Oxybutynin

Tolterodine which is not funded by Pharmac in NZ, has an efficacy similar to oxybutynin, but has fewer side effects, hence more patients can tolerate the drug in the longer term.

Level of evidence 1.⁵⁶

Long-acting forms of both tolterodine and oxybutynin are available overseas, and had been shown to have fewer side effects than the immediate-release formulations.⁵⁶

4. Inflammation of the bladder

Treatment of the underlying cause can be effective in some cases. Patients with chronic pelvic pain syndromes presenting with symptoms of interstitial cystitis may improve with local therapies outside the scope of this report. However some will require urological advice and some of them will need to go on to surgical or other interventions.

Clinical questions addressed by the Development Team

Summary of Answers.

1. *What is bothersome nocturia?*

Nocturia is defined as the need to get up at night from sleeping, in order to pass urine. The number of times the person is awakened will influence the amount of bother experienced, but there is individual variation. If a person is not bothered, then usually there is no need to evaluate further unless it is in the context of other clinical problems.

2. *What are the important treatable causes of nocturia?*

These have been addressed in the body of the document #3.1 a,b.

3. *How do sleep disorders impact on nocturia?*

This topic was addressed in Section 3.1 xii.

4. *Does nocturia increase the risk of falls in the elderly?*

Yes. See Section 3.1 xii, and reference³⁷

5. *Which patients with what conditions, can be treated in Primary Care?*

This has been addressed throughout the document.

6. *What investigations should be done before treating a patient with nocturia in a primary care setting?*

These too have been addressed in sections #3.1 and #3.3

7. *Which patients need referral?*

Patients with any haematuria,

UTIs which fail to resolve in the expected time with appropriate therapies, or those with recurrent UTIs.

Any patient with a pelvic mass or prolapse

Patients in whom initial therapy has not helped within a reasonable time frame.

Men with a strong family history of prostate cancer, or who have a fear of it

8. *Can daytime life-style changes and daytime bladder retraining, reduce nocturia?*

There is Level 4 evidence that these measures can be effective in controlling the overactive detrusor. Section 4.3

9. *When is Desmopressin effective, and safe?*

It can be very effective in certain cases, where simple measures have failed.

Those over 65 years of age, and those with any congestive cardiac failure, or who have had hyponatraemia or symptoms suggestive, and those with polydipsia, should be excluded.

Hyponatraemia is the greatest risk, and in all cases the serum sodium and patient's weight should be checked, before and after 2-3 days of treatment.

RECOMMENDATIONS

A diagnosis and thence a treatment plan can often be reached after taking the first step of clinical evaluation with history and examination, and the second step with simple urine tests. Some patients with disorders discussed in the document like haematuria will have been identified, and will have required referral to a specialist for urgent advice. Others will respond to lifestyle advice and require no further action.

For those continuing with problems, or for whom a diagnosis has not been reached, then the bladder diary (step 3) will help to identify the presence of excessive urine production either throughout the day and night, or limited to night-time. It will also identify patients who have an overactive bladder syndrome with reduced functional bladder capacity. Some can be managed along the lines suggested, while others will require referral for specialist advice.

ALGORITHM

The above guideline has been incorporated into an algorithm recommended for use in NZ. (Appendix 4)

APPENDIX 1 MEMBERSHIP OF NOCTURIA GUIDELINE COMMITTEE

Arnold EP(Chair)	Urologist	Christchurch School of Medicine
Boulton J	Urologist	Auckland
Brown J	Urotherapist	Hamilton
Catherwood A	Primary care physician	Auckland
Croker T	Primary care physician	Auckland
Harris R	Geriatrician	Auckland

Mark SD	Urologist	Christchurch
Robson R	Renal physician	Christchurch
Weatherall M	Geriatrician	Wellington School of Medicine

**APPENDIX 2 GRADING OF EVIDENCE
ICUD Modification of the Oxford System**

- Level 1. Randomised Controlled Trial (RCT)
2. Prospective cohort study
3. Retrospective case controlled study
4. Case series
5. Expert opinion

Grades of evidence for investigations need to include:
 Technical performance
 Diagnostic performance
 Clinical value

APPENDIX 3 BLADDER DIARY

BLADDER DIARY

Input: Record the type and volume of all fluids drunk

Output: Record the time and volume of all urine you pass during the three days and nights of this diary record.

Leakage episodes: Record any leakage of urine and the circumstances and whether you felt any desire to pass urine just before the leakage occurred.

SAMPLE

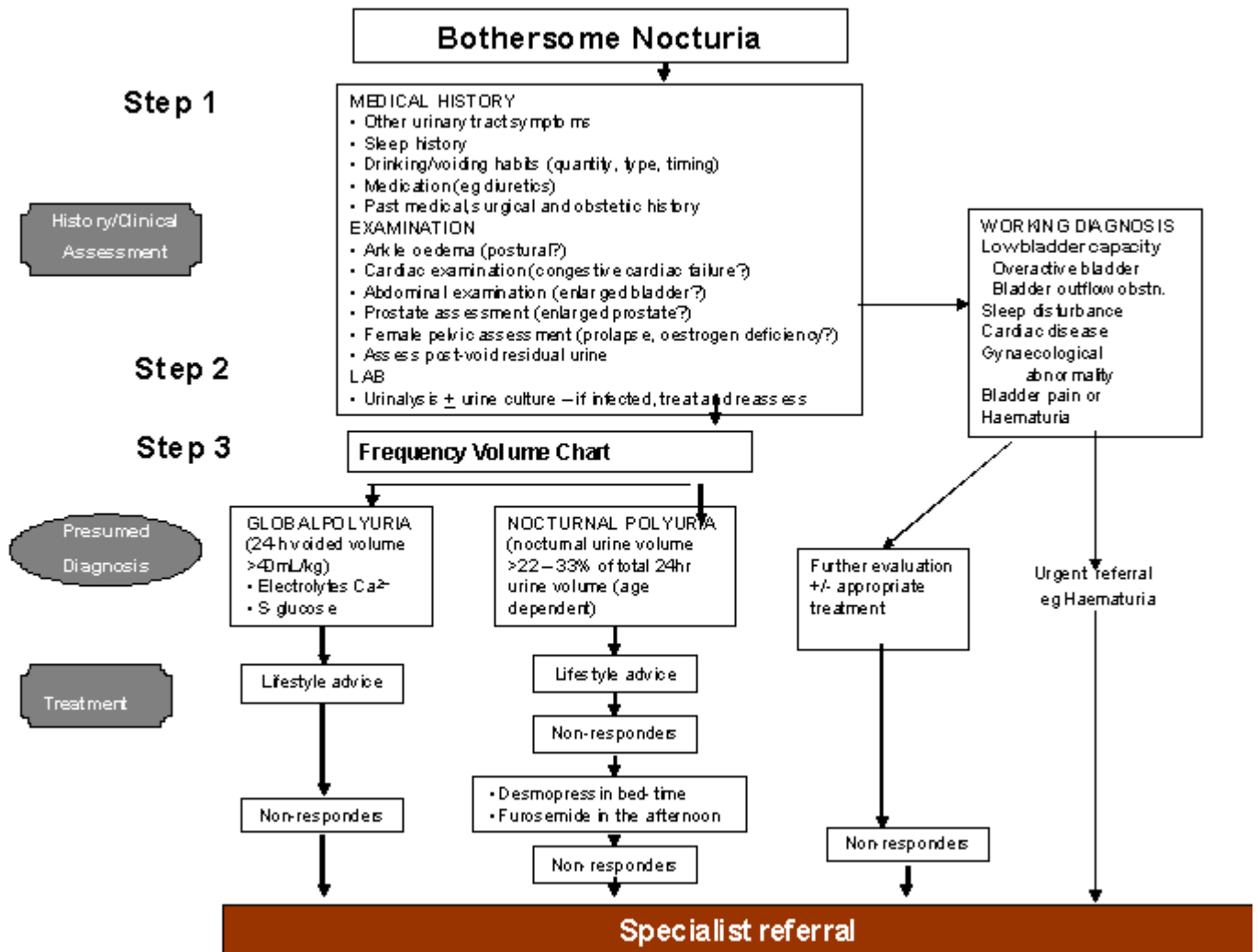
Date:

Time	Drinks and volume	Urine Volume measured(mls)	? Any leakage circumstances	?with urgent feeling	Comments	Type
0800	tea one cup					
0830		200 mls				
1000			Leaked with cough		Nil	
1030	Coffee one cup					
1130		300				

Continue day and night for three days and nights.

APPENDIX 4

Algorithm modified from International Guideline



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