IDC/Atonic Bladder Background and Current Treatment Options

The inFlow's pivotal study (conducted under IDE G970029) was limited to women with a urodynamically confirmed diagnosis of atonic bladder. (Atonic bladder was the term commonly used to describe impaired detrusor contractility or IDC at the time the study was conducted and so will be used in this document.) This document reviews the following topics related to IDC/atonic bladder: 1) the lack of standardized terminology, 2) causes and medical consequences and 3) current treatment options and their limitations.

This document is largely concerned with the medical aspects of IDC/atonic bladder, but the personal consequences of this condition must also be considered. The ability to control voiding is basic to our sense of identity. We are born without that ability, most gain it as children and many lose it before they die. As a result, some view this state (correctly or not) as an end-stage development. As crucial as this sense of control is, most women with IDC/atonic bladder have no hope of regaining it. Although most of their energy is consumed with their primary medical condition (stroke, MS, spina bifida, SCI, etc.), the inability to spontaneously void is often cited as the most bothersome part of their lives.

A.1 Terminology

Atonic (or acontractile) bladder is a medical condition where patients are unable to spontaneously urinate due to insufficient detrusor muscle contraction, usually due to neurologic disease or injury. That seems like a straightforward description, but there is a longstanding lack of standardization in the diagnostic terminology used to describe these patients. Although the inFlow's pivotal study imposed a level of rigor to its inclusion criteria by limiting subjects to those with "a urodynamically confirmed diagnosis of atonic bladder," in clinical practice patients with similar voiding difficulties are routinely assigned a diagnosis described by any of the following: a) symptoms (e.g., urinary retention or overflow incontinence), b) related co-morbidities (e.g., stroke, multiple sclerosis, diabetes, spina bifida) or c) underlying anatomic deficiencies as observed or presumed (e.g. impaired detrusor contractility or detrusor-sphincter dyssynergia, although the latter is less common in women).

In 2009, "An International Urogynecological Association (IUGA) / International Continence Society (ICS) Joint Report on the Terminology for Female Pelvic Floor Dysfunction" [1] attempted to provide some standardization in terminology, suggesting use of the phrase "voiding dysfunction." Many clinicians considered this term too vague; however, and even the IUGA/ICS report offered an alternative presentation, "*chronic retention of urine:* This is defined as a non-painful bladder, where there is chronic high PVR (post-void residual)."

It is not surprising, but worth noting that the variability in diagnostic terminology makes it difficult to accurately estimate the prevalence of women with atonic bladder/voiding dysfunction.

A.2 Causes and Medical Consequences

As a result of having atonic bladder, patients are likely to experience urinary retention and/or incontinence. Often patients suffering from atonic bladder require caregiver assistance because they have additional disabilities that prevent them from caring for themselves.

Causes of atonic bladder include intrinsic damage to the detrusor muscle due to trauma (*i.e*., spinal cord injury and vaginal birth delivery), or systemic diseases, including central nervous system disorders or peripheral damage to the nervous system (*i.e.,* spina bifida, multiple sclerosis, and diabetic neuropathy). [2-8] Atonic bladder also occurs in patients with hyperreflexic bladder in whom anticholinergic drugs cause iatrogenic atonic bladder (*i.e*., in patients with multiple sclerosis). [6, 8]

Patients with atonic bladder typically suffer from chronic retention, "an insidious failure of bladder emptying that results in at least 50 percent of maximum cystometric capacity being retained."[9]

They may also experience overflow incontinence, a painful and dangerous situation where the bladder is filled and stretched to its maximum and yet the patient is unable to void. Many patients with atonic bladder also suffer from painful recurrent urinary tract infections due to bacterial growth in a pool of stagnant urine in the bladder. [10]

A.3 Current Treatment Options

Not only is atonic bladder often progressive and generally incurable, there are very few clinical alternatives. Currently no surgical or pharmaceutical remedies exist for atonic bladder. Although sacral neuromodulation (SNM, available as the brand name Medtronic InterStim®) has shown positive results for certain non-obstructive retention, SNM is appropriate only for patients with hyper-tonicity of some sort, such as Fowler's Syndrome [11,12]; it is not useful for retention due to hypo-tonicity and therefore is not helpful for atonic /acontractile bladder patients. While alpha blockers help coordinate function between the bladder and sphincter, the fact that they also relax the detrusor muscles makes this of limited value to individuals with an atonic bladder.

The standard management modalities for patients with atonic bladder, as described in the AHCPR Clinical Practice Guideline for Urinary Incontinence in Adults, are intermittent catheterization, indwelling (Foley) catheterization, or surgery (suprapubic tube cystostomy). [6] Patients with insufficient bladder contractions generally require urinary catheterization to prevent the occurrence of urinary retention and its attendant complications, and to prevent episodes of overflow incontinence. [2] Therefore, catheterization is generally considered the treatment method of choice for patients with atonic bladder, despite the often high rates of infection and invariably low quality of life:

- UTIs from urinary catheters are quite common, but their full impact is not well understood, even by most healthcare providers. [13] Per CDC estimates, catheter-related UTIs cause over 13,000 deaths and add $1.85 Billion in direct medical costs annually in U.S. hospitals alone. [14] This estimate is notable for its limited scope: a) it includes only patients with indwelling catheters; b) it does not include community-dwelling catheter users or those in assisted living or long-term care facilities; and c) it is based on the most recent year with completed data, but that year is 2002. In a worrisome trend, the risk from catheter-related UTIs is increasing with the emergence of resistant bacteria, while attempts to improve the infection resistance of urinary catheters with bactericidal coatings, etc. have been only modestly successful. [15, 16] As a result, it is likely that UTI-related mortality has increased or will increase.[17]
- Chronic catheterization can be psychologically devastating. Either patients are literally tied to a bag of their own urine, which many regard (correctly or not) as an end-stage development, or they must self-catheterize, a procedure that is so burdensome its long-term compliance is low.

Because of these problems, clinical practice restricts use of urinary catheters only to those patients who need them and only for as long as they need them. In general, four types of catheters are used: indwelling (Foley), intermittent, suprapubic and condom catheters. Suprapubic catheterization is a surgical procedure, which restricts its use. ("It is undertaken where a total blockage of the urethra or prostatic urethra has occurred or where urethral catheterization cannot be undertaken.") [18] Use of condom catheters is obviously limited to men.

That normally leaves only two options for women, indwelling or intermittent catheters. The choice between these two depends on multiple factors, including the medical condition, treatment objectives, healthcare setting and even the preference of the patient.

All known catheter-related problems are exacerbated for atonic bladder patients, since they must either catheterize multiple times daily or live with an indwelling catheter for the rest of their lives.

A.3.1 Intermittent Catheterization (CIC)

Intermittent catheterization has become a standard treatment for persons with spinal cord injuries and for patients with other forms of chronic urinary retention due to an underactive or atonic bladder. [19, 20] This procedure can be performed by patients or their caregivers using sterile or clean catheters to provide intermittent routine bladder emptying every three to six hours.

Clean intermittent catheterization (CIC) is generally regarded as the preferred option for chronic bladder drainage, since it can provide patients with the ability to self-manage their voiding and is known to have a significantly lower UTI rate than indwelling (Foley) catheters. A central advantage to CIC is that it costs only a quarter of that spent on sterile intermittent catheterization (SIC) with virtually the same safety and efficacy.[21] Appropriate CIC technique stresses the importance of frequency of catheterization over sterility.

Advantages of intermittent catheterization over indwelling (Foley) catheterization include better patient acceptance by allowing the patient more independence, improved hygiene, elimination of a persistent foreign body sensation, ease of sexual relations, and less frequent hospitalization due to fewer complications. [22-27] Long term use of intermittent catheterization appears to result in fewer complications, such as infections and bladder and renal stones, than does chronic indwelling catheter use. [26-31] Reduced rates of sepsis and urinary tract infection are often associated with frequent intermittent catheterization where excessive residual urine in the bladder can be minimized. Unfortunately, however, well-designed comparison studies have not been performed. [28, 31]

Despite these advantages, numerous complications are nevertheless associated with intermittent catheterization. Such complications include urethral strictures, false passages, hematuria, vesicoureteral reflux, hydronephrosis, bacteriuria, urinary tract infection, labial erosion and poor voiding potential. [3, 22, 28, 32, 33, 34, 35, 36] Additionally, CIC requires urethral insertion of a catheter 4-8 times per day (>120 times per month), and so is practical only for those capable of self-catheterization. Since CIC can result in urethral trauma even when performed by those with experience, it is not at all suited to patients with restrictions in manual dexterity, vision or cognitive ability (i.e. many women with atonic bladder). While intermittent catheterization may be used by paraplegics, the blind, elderly, and the mentally handicapped, patients often require the assistance of caregivers, with attendant reliance on others and associated inconvenience and embarrassment.

Finally, even patients who are able often choose not to perform CIC, as it can be a time-consuming, malodorous procedure; 33% of patients (mostly women) report their experience with this method to be aversive, [37-40] as it requires a high level of manual dexterity and causes discomfort and distress. [23, 28, 41, 42] Elderly patients in particular opt for Foleys despite their risks, possibly due to reluctance to repeatedly touch their genital area. [43] These factors often lead to psychosocial problems and contribute to diminishing quality of life for patients with atonic bladder.

A.3.2 Indwelling (Foley) Catheters

An indwelling urethral catheter is a closed sterile system inserted through the urethra to allow bladder drainage. The indwelling catheter is retained in the bladder for days or weeks at a time and therefore has an advantage over intermittent catheterization in that it requires little patient cooperation or assistance at home. This infrequent insertion also has another advantage over intermittent catheterization in that it decreases the possibility of injury to the urethra or bladder associated with repeated insertion.

These are the single most commonly used type of urinary catheters. Foley catheters are medically necessary for bladder drainage during surgery and post-operative tracking of urine output; however, they are frequently used on a long-term basis in nursing homes and elsewhere as a matter of convenience.

However, long-term use of indwelling catheters is a significant cause of bacteriuria and urinary tract infection. [6, 10] Patients with long-term indwelling catheters almost always develop a chronic bacteriuria. [10] Bacteriuria arises at the rate of about 3 to 10 percent per day [10], approaching 100% infection in 30 days). [44-46] Also, prolonged use of Foleys causes the bladder to shrink and become non-compliant, and even short-term use can cause problems, particularly in elderly patients. [47] These patients frequently remain on Foley catheters indefinitely. In addition to their medical consequences, Foley catheters also negatively affect the self-image of patients.

Encrustations form inside indwelling catheters persistently over time among some patients, while they are virtually never found among some other patients. [48] Patients who consistently and repeatedly develop extensive encrustation on their urinary catheters are called "blockers." [48] Blockers require catheter changes at shorter intervals despite the use of large bore catheters since the encrustation decreases the urine flow-rate. [48] Although the management of indwelling catheters in these cases varies (depending on the urine flow-rate), the usual practice is to change indwelling catheters every 30 days. [6] A decreased urine flow-rate is a common indication of encrustation formation. [6] However, there is no data available on the optimal frequency of catheter changes. [16]

Scanning electron microscopy has been used to show that encrustation on urinary catheters is associated with bacteria which colonize the catheter surface. [49] The encrusting deposits consisted of struvite crystals surrounded by aggregates of very small crystallites of hydroxyapatite. [49] A layer of bacteria associated with the crystals may protect both the bacteria from antibiotics and the crystals from acidic bladder washout solutions intended to dissolve them. [49]

The development of silver-coated, antimicrobial, lubricious-coated Foley catheters may decrease the formation of encrustation and other complications, however, further research is needed with these products to determine their effectiveness. [50-55] Several types of catheter materials (*e.g.*, silicone, latex, Teflon), have been tested, however, silicone catheters tend to lead to less encrustation than Teflon or latex catheters. [48, 56]

Indwelling catheters may cause a range of histologic changes in the bladder, including irritation of the bladder wall that can result in microscopic hematuria. [32] Polypoid cystitis is a chronic, nonneoplastic inflammatory condition that occurs in most patients with indwelling catheters in place for more than a month. [32] Patients who utilize indwelling catheters for years are at risk for the development of squamous cell carcinoma. [32] The bladder wall can also be damaged by an indwelling catheter through a variety of mechanisms, eventually leading to perforation of the bladder. [32] Other complications associated with indwelling catheters include obstruction secondary to encrustation, uncontrolled urine leakage, catheter extrusion, unprescribed removal through patient non-compliance, bladder spasms, urethral erosion, bladder and renal stone formation, periurethral abscess, chronic renal inflammatory changes, hematuria, bacteriuria, sepsis, and urinary tract infections. [48, 56, 57, 58, 59]

A.3.3 Suprapubic Tube Cystostomy

Suprapubic tube cystostomy involves percutaneous or surgical introduction of a tube into the bladder through the anterior abdominal wall. This type of surgery is contraindicated in persons with chronic unstable bladder and urethral sphincter insufficiency. [6] The suprapubic tube cystostomy is preferable to an indwelling catheter in the patient with urethral complications who requires chronic bladder drainage and for whom no other alternative therapy is possible. [6]

Immediate complications of suprapubic tube cystostomy include infection, cellulitis, hematoma, and bowel injury. [6, 60, 61] Long-term complications are similar to those associated with the use of indwelling catheters. [60, 61] In addition, there are potential problems with the management of suprapubic tube cystostomy, such as uncontrolled urine leakage, and skin erosion. [6] There is also a perceived problem with long-term medical management of suprapubic tube cystostomy due to lack of

knowledge and expertise of health care professionals and lack of quick access to medical care by the homebound patient if a problem arises. [6] Therefore, suprapubic tube cystostomy is often a choice of last resort for patients with atonic bladder who fail to respond to all other methods of treatment.

A.4 Bacteriuria and Urinary Tract Infections

Bacteriuria, which may be caused by encrustation formation of mineral and bacteria complexes, develops in most persons within two to four weeks after indwelling catheter insertion. [29, 49, 56, 59, 62] Bacterial counts increase the longer an indwelling catheter remains in place. [29] Bacteriuria also develops in 50 to 60 percent of patients using clean intermittent catheterization in the absence of antibiotics. [33, 63] As a general rule, the use of long-term suppressive therapy with antibiotics in patients regularly using catheterization is undesirable because it is associated with the emergence of resistant bacterial strains. In addition, no measure (*i.e.*, antibiotic irrigation of the catheter, antibiotics in the drainage bag, antibiotic compounds at the meatus or systemic antibiotics), has been shown to consistently prevent bacteriuria. [32] While bacteriuria is often asymptomatic, if it progresses to clinical UTI it can be associated with fever, bacteremia, and death. [29]

Nosocomial urinary tract infection is the most common hospital-acquired infection in the United States, [32] and most cases are associated with an indwelling catheter. [59] This common complication of urethral catheterization is also potentially the most serious. Cases of sepsis and death from severe urinary tract infections due to indwelling catheter complications have been reported. [30] Among those with indwelling catheters in a nursing home population, mortality was three times higher than in non-catheterized patients, with significantly increased mortality in catheterized females. [64, 65]

Attempts to improve the infection resistance of urinary catheters with bactericidal coatings, etc. have been only modestly successful, at best delaying, but not preventing UTIs. [16] In fact, Stickler and others maintain that these coatings have yet to prove they have any effect on clinical UTIs:

> "The trials reported in the literature have generally used the mere presence of bacteria in the urine at various levels from >100/ml to >100,000/ml as the criteria of infection. Trautner et al. were critical of this approach and expressed the view that clinical trials simply using bacteriuria, at whatever level, as the criterion for infection are fundamentally flawed. They considered that it is important to appreciate the distinction between urinary tract infection and asymptomatic bacteriuria in order to attempt a rational assessment of the evidence from these trials. The mere presence of bacteria in the urine of catheterized patients who are asymptomatic, is a quite different situation from that in which bacteria are present in the urine and the patient is exhibiting symptoms indicating that invasion of the tissues of urinary tract has occurred." [15]

The confusion between elevated bacteria levels and clinical UTI is also causing problems in clinical practice. Inappropriate treatment of asymptomatic bacteriuria is exposing large numbers of patients to the risk of adverse drug events, particularly in nursing homes, and is encouraging the growth of antibiotic resistant organisms. [16]

The prevalence of symptomatic urinary tract infections in women performing clean intermittent catheterization ranged from 12 to 17 percent. [28, 63] Infections that do occur with clean intermittent catheterization are usually managed without further sequelae, provided vesicoureteral reflux does not exist, and bladder overdistension and trauma are avoided. [36, 66, 67] Therefore, frequent bladder voiding and turnover in catheter replacement can help to reduce the incidence of urinary tract infections.

A.5 Summary of Current Treatment Options

Women with atonic bladder are coping with difficult circumstances and quality of life is in short supply. For most, their atonic bladder is secondary to a life-altering condition such as spina bifida, multiple sclerosis, stroke, spinal cord injury, or diabetic neuropathies. Also, they tend to be elderly and many have cognitive deficiencies. The urinary dysfunction for many atonic bladder patients is progressive, devolving steadily and irreparably. Those patients require regular and repeated evaluations for management. Those who live long enough face functional challenges associated either with their underlying disease and/or the aging process, both of which heighten the challenge of effective bladder management. For example, the impaired functioning of large and small motor skills among patients with Parkinsonism and MS inevitably worsens urinary function. Deteriorating dexterity, balance, physical flexibility and vision associated with disease progression and aging further complicate the management challenge.

Since atonic bladder and the urinary dysfunction that it causes are often progressive and generally incurable, they must be managed. Effective bladder management options are critical.

Currently, the vast majority of atonic bladder patients use urinary catheters. All known catheter-related problems are amplified for atonic bladder patients, since they must either catheterize multiple times daily or live with an indwelling catheter for the rest of their lives. Although CIC is generally considered a medically adequate solution, not all women can or will self-catheterize. Clinicians who work with this population report that, despite the fact that all women with atonic bladder are strongly urged to use CIC due to the very high rate of UTI associated with Foley use, the majority eventually end up with Foleys. Also, even women who can use CIC are in need of improved quality of life.

As a result of these and other deficiencies with current treatment options, there is an urgent need for improved methods of bladder drainage for women with atonic bladder.

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    Note: The website for the Centers for Disease Control and Prevention (CDC), as accessed on 12-29-08, estimates the number of deaths related to UTIs from urinary catheters to be 32,000 for U.S. hospitals in 2002: http://www.cdc.gov/ncidod/dhqp/hai.html
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