

inFlow™ Urinary Prosthesis: Claims of Significant Therapeutic Distinction

Although urinary catheters are very commonly used, they are known to cause serious problems, particularly with chronic use, specifically:

1. Urinary tract infections (UTIs)
2. Low quality of life
3. Encrustation

These problems are acutely heightened women with impaired detrusor contractility (IDC) of neurologic origin, since their bladder function has been permanently impaired by their neurologic disease or injury (MS, spinal cord injury, stroke, spina bifida, etc.) and they must use urinary catheters on a life-long basis to prevent the occurrence of urinary retention and its attendant complications and to prevent episodes of overflow incontinence.ⁱ

The present standard of care for women with IDC is clean intermittent catheterization (CIC) and the most common alternative is indwelling (Foley) catheters. Long-term use of CIC appears to result in fewer complications, such as infections and bladder and renal stones, than does chronic indwelling catheter use.^{ii,iii,iv,v,vi,vii}

The following three sections compare the performance of these urinary catheters to that of the inFlow with regard to the most serious catheter-associated problems.

1. Urinary Tract Infections (UTIs)

The inFlow's low rate of UTIs is its most significant therapeutic distinction. The inFlow's pivotal trial showed it to have a lower rate of UTIs than clean intermittent catheterization (CIC), the current standard of care. This was a significant enough finding that the FDA put out a news release when it approved the inFlow and its Chief Scientist for devices, Dr. Maisel, made the following statement:

"It is noteworthy that the most significant of adverse events – UTI – appears to occur at a lower rate with the inFlow device as compared to CIC." –FDA 10-14-2014 News Release^{viii}

Importantly, the inFlow can also be used not only by women who use CIC, but also by those who use indwelling (Foley) catheters, which are known to have an exceedingly high rate of UTIs. These women are at significant risk of life-threatening (and expensive) infection:

- Women who use Foley catheters on a chronic basis suffer multiple UTIs annually.
- In at least 5% of these women, a UTI will progress to urosepsis.
- As many as 40% of those women will die as a result.

UTIs from urinary catheters are quite common, but their full impact is not well understood, even by most healthcare providers.^{ix} Per CDC estimates, catheter-related UTIs cause over 13,000 deaths and add \$1.85 billion in direct medical costs annually in US hospitals alone.^x These estimates are notable for their limited scope: a) they include only patients with indwelling catheters; b) they do not include community-dwelling catheter users or those in assisted living or long-term care facilities; and c) they are based on the most recent year with completed data, but that year is 2002.

In a worrisome trend, the risk from catheter-associated 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 if at all successful.^{xi,xii} As a result, it is likely that UTI-related mortality has increased or will increase.^{xiii} Clearly, the best (and most cost effective) treatment for infection is prevention.

Its 18-site ($n=273$) pivotal trial showed the inFlow to have superior infection resistance to the current standard of care. The inFlow's pivotal trial was a LOE Ib study conducted under IDE that compared not only the safety and effectiveness, but also the user experience of the inFlow device versus CIC, the current standard of care for long-term bladder drainage. This study utilized a crossover design in which each subject served as her own control and was limited to women with a urodynamically confirmed diagnosis of atonic bladder (IDC) who were successfully using CIC (some for as long as 20 years). Subjects' CIC use was monitored for eight weeks to establish a Baseline and then they were crossed over to 16 weeks of inFlow Treatment. Findings concerning UTI rates were as follows:

UTI rates for the inFlow started off slightly lower than for CIC and *declined* with continued use (CIC Baseline=0.12, first half of InFlow Treatment period=0.11 and second half of inFlow Treatment period=0.08).

The UTI experience in this study is based on 417 patient-months of cumulative exposure in 157 patients; thus, the UTI rate observed is a representative and robust estimate of what is expected in clinical use.^{xiv}

The inFlow's infection resistance is thought to result primarily from its ability to mimic normal voiding behavior by providing periodic, forceful, and complete evacuation of urine. In contrast, a Foley catheter does none of these things. Both the inFlow device and CIC maintain the normal urine fill-void cycle, which in turn preserves bladder tone, and both effectively empty the bladder; however, only the inFlow provides turbulent evacuation of the urine, maintaining the flush mechanism that the body normally uses to protect itself against bacterial buildup. Also, the inFlow is a sterile device that is inserted only once per month, whereas CIC requires 4-6 insertions daily, each of which is an opportunity to introduce bacteria. Finally, the inFlow device is inserted using a sterile introducer and, after insertion, is almost entirely contained within the urethra, minimizing hand contact and other opportunities to introduce bacteria.

2. Low Quality of Life (QoL)

Most users regard the inFlow's ability to improve quality of life as its greatest benefit. Its pivotal trial showed that the inFlow improved QoL by almost 60% compared to CIC, the current standard of care,^{xv} and an investigator-sponsored one-year study showed that it improved QoL by 80%.^{xvi}

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.

As previously noted, the present standard of care for women with IDC is CIC; however, since CIC requires a tube to be inserted into the bladder 4-6 times per day, it is only practical if a woman can self-catheterize. Unfortunately, many women with IDC either cannot or will not self-catheterize. Many lack the visual, manual, or cognitive ability to safely perform this procedure due to age and/or their primary medical condition. Others choose not to. Many women, particularly the elderly and the sexually abused, are reluctant to repeatedly touch their genital area. If a woman cannot or will not use CIC, then she is likely to end up with a Foley catheter and urine drainage bag, despite the high rate of UTIs and low quality of life that invariably result.

For women with IDC, any review of their clinical options is a reminder of their psychological as well as medical circumstances. Despite the very serious nature of their primary medical conditions, most will state that the inability to void normally is the most bothersome part of their daily lives, as this ability is basic to a sense of independence from the time we are small children. To lose this control has important psychological consequences. Many who lose it as adults view it as a demarcating event, signaling the end of their normal adult lives and the start of dependency. As crucial as it is, women with IDC currently have almost no hope of regaining the ability to void normally.

As a prosthetic device, the inFlow's clinical objective is to normalize voiding to the greatest degree possible. This results in tangible benefits that are meaningful to its users, including:

- a) eliminating the need to self-catheterize multiple times daily;
- b) eliminating tubes and bags, improving body image and hygiene;
- c) allowing most users to void without assistance, increasing self-reliance; and
- d) allowing use of a toilet, a psychologically significant benefit as that is the "normal" way to void.

The inFlow's ability to restore functional capacity and personal dignity to its users has been documented by numerous letters from physician experts and patients' family members:

"The inFlow device is truly remarkable in its ability to virtually restore the functional behavior of the urinary bladder. No other product, drug, or device can accomplish this to the same degree. The device should be given a high priority consideration for all female patients having difficulty emptying their bladders." - Richard Schmidt, MD, inFlow Clinical Investigator and Co-inventor of the Medtronic Interstim

"It can simply, yet absolutely transform the quality of lives." - Patient's Brother

"(The inFlow is) an unqualified success. It is difficult to put into words the effect it has had on (my daughter's) life." - Patient's Father

3. Encrustation

A study by D. Stickler of the Microbiology Research Group at Cardiff University (UK) showed the inFlow prosthetic device's encrustation resistance to be at least 8.4 times better than a silicone Foley catheter, the current gold standard.^{xvii}

"Under conditions that simulated a heavy infection of P. mirabilis, where a conventional Foley catheter blocked with crystalline biofilm after 25.7 hours, the inFlow device drained the bladder for at least 9 days... (and its) central lumen appeared to be essentially clear."

In addition, there was no encrustation reported in the inFlow's pivotal trial.

Encrustation is perhaps the most commonly encountered clinical problem with indwelling urinary catheters, and about 50% of all patients with indwelling catheters experience problems with blockage due to encrustation. This is distressing to patients and can result in urine leakage around the catheter, urinary retention, and pain on removing of the catheter, a procedure that can also result in urethral trauma.^{xviii}



Figure 7-1: Indwelling catheter with encrustation

This problem has proven quite difficult to resolve:

"In an attempt to avoid the development of encrustation, various measures have been tried, including the use of long-acting antimicrobial coatings, and treatments designed to detach biofilms as they form. Currently however, these measures are far from perfected, and encrustation will remain a significant problem for indwelling catheters for the foreseeable future."^{xix}

The inFlow's encrustation resistance is thought to result primarily from its ability to provide turbulent evacuation of the urine, maintaining the flush mechanism that the body normally uses to protect itself against bacterial buildup.

Safety and Effectiveness

Its pivotal study clearly established the safety and effectiveness of the inFlow urinary prosthesis.

- Safety: No serious or long-lasting adverse events were reported and the inFlow showed a lower rate of urinary tract infections than clean intermittent catheterization (CIC), the current standard of care.
- Effectiveness: 98% of evaluable subjects met the primary clinical endpoint, which was to effectively drain the bladder as determined by measurement of post-void residuals. The inFlow also improved quality of life, the secondary clinical endpoint, by almost 60% compared with CIC.

Clinically minor adverse events are routine with all methods of bladder drainage; however, no serious or long-lasting adverse events associated with inFlow device use have been reported in over a decade of clinical use. Documentation of clinical use includes the following:

- The inFlow's pivotal trial ($n=273$), which was the primary evidence for FDA review.
- Six investigator-sponsored studies (total $n=228$ subjects), three of which were long-term studies of 1-4 years and all of which were published in peer-reviewed journals.
- ISO-audited Complaint Files concerning >12,000 devices used outside the U.S. At one device per month, this amounts to >1,000 women years of clinical use.

References Cited

- i Bowen LW. *Voiding Dysfunction*. *Ob and Gyn Clinics of N Amer* 16: 869-882 (1989).
- ii Timoney AG, Shaw PJR. Urological Outcome in Female Patients with Spinal Cord Injury: The Effectiveness of Intermittent Catheterisation. *Paraplegia* 28: 556-563 (1990).
- iii Joiner E, Lindan R. Experience with self intermittent catheterization for women with neurological dysfunctions of the bladder. *Paraplegia* 20:147-153 (1982).
- iv Bakke A. Physical and Psychological Complications in Patients treated with Clean Intermittent Catheterization. *Scand J Urol Nephrol Suppl* 150: 1-69 (1993).
- v Tenney JH, Warren JW. Bacteriuria in Women with Long-Term Catheters: Paired Comparison of Indwelling and Replacement Catheters. *J Infectious Diseases* 157: 199-202 (1988).
- vi Vaidyanathan S, Rao MS, Saleem A, Subudhi CL, Rajendran LJ, Shrikhande VV. Fatal intra-peritoneal bladder rupture due to blocked catheter in a paraplegic. *Paraplegia* 17: 272-277 (1979).
- vii Webb RJ, Lawson AL, et al. Clean intermittent self-catheterization in 172 adults. *Br J Urol* 65: 2023 (1990)
- viii FDA News Release "FDA permits marketing of urinary prosthesis device for women." Oct 14, 2014
- ix Saint S, Kowalski CP, Kaufman SR, Hofer TP, Kauffman CA, Olmsted RN, Forman J, Banaszak-Holl J, Damschroder L, Krein SL. *Preventing Hospital-Acquired Urinary Tract Infection in the United States: A National Study*. *Clinical Infectious Diseases* 2008; 26:243-250
- x Klevens RM, Edwards JR, Richards CL, Horan TC, Gaynes RP, Pollock DA, Denise M. Cardo DM. *Estimating Health Care-Associated Infections and Deaths in U.S. Hospitals, 2002*. *Public Health Reports*; March–April 2007; 122:160-166.

- ^{xi} Stickler, D. *Comment re: Types of urethral catheters for management of short-term voiding problems in hospitalized adults*. *Neurourology and Urodynamics*, 27: 748. doi: 10.1002/nau.20647 (2008)
- ^{xii} Centers for Disease Control and Prevention (CDC). *Guideline for Prevention of Catheter-Associated Urinary Tract Infections 2009*. <http://www.cdc.gov/hicpac/pdf/CAUTI/CAUTIguideline2009final.pdf>
- ^{xiii} Johnson JR, Kuskowski MA, Wilt TJ. *Systematic review: Antimicrobial urinary catheters to prevent catheter-associated urinary tract infection in hospitalized patients*. *Ann Intern Med* 2006; 144(2):116-126
- ^{xiv} FDA DEN130044 Vesiflo inFlow *de novo* Summary
- ^{xv} Vesiflo Direct *De novo* Petition: inFlow[™] Intraurethral Valve-Pump. October 22, 2013
- ^{xvi} Lynch WJ, Testa GA, Bell D: *A Study to Determine Subjective and Objective Benefits of a Remote-Controlled Intra-Urethral Device for the Management of Female Acontractile Bladder*. *Brit J Urol* 2003; 92: 960-963.
- ^{xvi} Getliffe K. *Managing recurrent urinary catheter encrustation*. *Br J Community Nurs* 2002; 7:574,576, 578-580.
- ^{xvi} Webber R. *Advances in Urinary Catheter Technology*. *Urology News*. May 2003.
- ^{xvi} Stickler D. *Operation of inflow in Proteus mirabilis infected in vitro bladder models*. Unpublished. Conducted at Microbiology Research Group, Cardiff University, UK. 2004.