
Research priorities for urological care following spinal cord injury: recommendations of an expert panel

K. C. Hayes, PhD, K. Bassett-Spiers, R. Das, BSc, K. D. Ethans, MD, C. Kagan, BA, J. L. K. Kramer, BSc, T. Linsenmeyer, MD, K. N. Moore, PhD, H. Razvi, MD, G. Reid, PhD, J. S. Walter, PhD, J. W. L. Wilson, MD

The Ontario Neurotrauma Foundation International Expert Panel

HAYES KC, BASSETT-SPIERS K, DAS R, ETHANS KD, KAGAN C, KRAMER JLK, LINSENMAYER T, MOORE KN, RAZVI H, REID G, WALTER JS, WILSON JWL. Research priorities for urological care following spinal cord injury: recommendations of an expert panel. *The Canadian Journal of Urology*. 2007;14(1):3416-3423.

Objective: A multidisciplinary panel of experts from Canada and the United States was convened by the Ontario Neurotrauma Foundation (ONF) to establish research priorities in the area of urological care following spinal cord injury (SCI).

Design: The panel reviewed a synthesis of published literature in five areas of urology, identified emerging opportunities in the private and public sector, and used a modified Delphi approach to reach consensus on priorities for funding.

Results: The panel recommendations included: clinical trials of the safety and efficacy of M₃ receptor specific anti-muscarinic agents for bladder hyperactivity in SCI patients;

development and testing of protocols for sacral nerve electrostimulation without sacral afferent neurectomy for management of micturition – including selective stimulation of sacral nerve fibers, high frequency blocking of the pudendal nerve to minimize the risk of urethral sphincter co-contraction and genital nerve stimulation for bladder inhibition and incontinence management; clinical trials of the efficacy and safety of intra-urethral valve catheters; trials of the efficacy of probiotics for bacterial interference i.e. to reduce colonization by uropathogens and manage the dual problems of infection and pathogen resistance to antimicrobials: innovations in the prevention or treatment of stone disease (ureteral, bladder and kidney).

Conclusions: The recommendations form the strategic priorities of the ONF SCI grants program for Ontario-based investigators and their partnerships with out-of-province collaborators and organizations.

Key Words: spinal cord injury, urinary tract infection, urology, probiotics, intermittent catheterization, kidney stones

Introduction

The Ontario Neurotrauma Foundation (ONF) is a Canadian health research funding organization established by the provincial government to enhance neurotrauma research. A key component of its strategic funding priorities is support of research into chronic disease management including secondary medical complications, such as voiding dysfunction,

following spinal cord injury (SCI). This area of research has been previously identified as integral to enhancing quality of life of persons with SCI.¹ In preparation for its 2006-2007 funding cycle, ONF sought the advice of an international expert panel to help establish a research agenda and priorities for funding in the area of urological care following SCI. The present report describes the process and outcomes from the deliberations of the panel.

Process for establishing the research agenda

Experts from the United States and Canada, in the fields of physiatry, urology, nursing, microbiology and physiology were invited to attend, together with a

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Address correspondence to Dr. Keith C. Hayes, Dept Phys Med & Rehab, Parkwood Hospital/SJHC, 801 Commissioners Road East, London, Ontario N6C 5J1 Canada

person with SCI and executive representatives of ONF. The membership, expertise and affiliations of the panel appear at the end of the article. Prior to the panel meeting, a literature search was undertaken to identify key areas of focus and to identify informative reviews within each area. The electronic databases of PubMed (National Library of Medicine & National Institutes of Health (USA) were searched using the MeSH terms; *bladder or bladder,neurogenic or urologic diseases and spinal cord injury*, for the years 1999-2005 and 366 articles were identified. The databases of CINAHL (for nursing and allied health literature) were also searched using additional MeSH terms of *urogenital disease, urinary tract infections and bladder management*. A total of 495 articles were retrieved of which 351 were deemed relevant. The articles were categorized into five *a priori* designated thematic areas that are described in Table 1. From each theme, key review papers were selected based on their currency, comprehensiveness and relevance to the theme. These research syntheses are identified below within the description for each theme. Health services research was not included as this area of focus is addressed elsewhere in the ONF research funding program.

The criteria used by the panel to establish the funding priorities were governed by the translational research policy of ONF (www.onf.org) which supports clinically relevant initiatives. These initiatives include late-stage animal or early-stage human clinical trials and may be based on existing evidence that points to the need for further investigation, or be innovative i.e. where published reports of clinical trials of efficacy are not yet available. In the course of panel deliberations, potential partnerships with industry were encouraged while recognizing the ethical

constraints of using public funds to support potentially "for profit" opportunities.

A modified Delphi consensus-building approach was used to identify the priority topics for funding within each theme. Rounds of discussion, followed by confidential voting, successively reduced the many potential areas of inquiry into identified priorities. The results of this iterative process now form the ONF research agenda for urological care. The summary that follows describes the pathophysiological context, the thematic areas and their associated discussion together with the identified priorities.

Pathophysiology of voiding dysfunction and associated urological complications

The panel identified the complexity of the pathophysiology of lower urinary tract dysfunction as a major consideration in the design of clinical trials for patients with SCI. For the upper motor neuron injured individual there are usually three problems: 1) detrusor sphincter dyssynergia (DSD), that is unwanted urethral contractions and obstruction during bladder contractions causing poor voiding and high bladder pressures, 2) an overactive bladder causing urinary incontinence and 3) a bladder that does not stay contracted long enough for effective bladder emptying. Some of the more common consequences of voiding dysfunction are the increased risk of urinary tract infection, upper tract stasis and the development of stones. All three of the pathophysiological conditions warrant consideration when evaluating new treatments for voiding dysfunction.

TABLE 1. Research priority recommendations from the expert panel

Focus	Recommendation
Pharmacological management of neurogenic voiding dysfunction	Clinical trials of the safety and efficacy of M ₃ receptor specific anti-muscarinic agents for bladder hyperactivity in SCI patients
Electrostimulation of bladder for micturition	Sacral nerve stimulation coupled with: <ul style="list-style-type: none"> - genital nerve stimulation for overactive bladder - pudendal nerve blocking for management of high urethral resistance
Devices and products for management of incontinence	Clinical trials of efficacy and safety of intra-urethral valve catheters Development and testing of novel external collection devices
Management of urogenital tract infection	Clinical applications of strains of avirulent bacteria (probiotics) that restore unbalanced flora and circumvent problem of uropathogen drug resistance
Medical and surgical interventions	Innovations in prevention or treatment of stone disease (ureteral, bladder and kidney)

Pharmacologic management of neurogenic voiding dysfunction

Pharmacologic interventions have typically focused on preserving continence, facilitating voiding and prevention or treatment of urinary tract infection. They may target central nervous system (CNS) pathways involved in micturition control, peripheral autonomic or somatic reflex mechanisms involved in storage or voiding, or have direct action on detrusor or sphincter muscles. Recent reviews of existing and potentially new pharmacologic interventions by Yoshimura et al,² Andersson and Pehrson,³ and Leippold et al⁴ helped inform the panel discussion.

Several CNS transmitters/transmitter systems are involved in the control of micturition but only a few centrally acting drugs have been used to treat voiding disorders in individuals with SCI.³ Gamma-aminobutyric acid (GABA), glutamate, opioid, serotonin, noradrenaline and dopamine receptors and mechanisms all contribute to the control of voiding and their respective roles are currently being elucidated. GABA agonists,^{5,6} alpha-2 adrenergic agonists,^{7,8} and dopamine agonists⁹ have been investigated in small scale trials in persons with SCI with promising outcomes. Other drugs that influence CNS function are being investigated in various animal models of voiding dysfunction and in early stage clinical trials.¹⁰ Some of these centrally acting drugs may thus provide novel targets for future pharmaceutical interventions in SCI patients.

Botulinum-A toxin is a presynaptic neuromuscular agent with indications for neurogenic detrusor overactivity, DSD, motor and sensory urge and chronic prostatic pain.⁴ Injections of botulinum toxin into the urethral sphincter have been shown to reduce the high urethral resistance that can be such a problem for individuals with SCI. In particular the injections can provide an important benefit for individuals using reflex voiding for their bladder management. In addition, botulinum toxin injection into the bladder wall can inhibit the bladder and reduce urinary incontinence. This is a potentially effective treatment for persons using intermittent catheterization.¹¹⁻¹⁷ Research is ongoing in this area with methodological issues (transperineal versus transurethral) being of interest; optimal dosing remains an issue of concern. The need for sufficiently powered, placebo-controlled clinical trials was recognized by the panel.

Following SCI the excitability of unmyelinated (C-fiber) bladder afferents is increased and contributes to neurogenic bladder dysfunction. C-fiber afferent neurotoxins such as capsaicin and resiniferatoxin block C-fiber activity and early stage clinical trials

with these agents resulted in increased bladder capacity and improved voiding.¹⁸ However, muscarinic receptor antagonists² remain the current first line of pharmacologic therapy to suppress detrusor hyperreflexia. These drugs act primarily by blocking post-junctional muscarinic receptors in the detrusor muscle; receptors that are normally activated by acetylcholine released from the parasympathetic postganglionic neurons. There exist four pharmacologically defined muscarinic receptor subtypes (M₁, M₂, M₃ and M₄) of which M₂ and M₃ exist in the human bladder smooth muscle.^{19,20} Nonselective antimuscarinic agents such as oxybutynin or tolterodine have been used extensively in the past to treat bladder hyperactivity.²¹⁻²⁴ Their efficacy is compromised by the side-effects of dry mouth, vision problems and constipation. The tolerability of these drugs have been improved by new modes of delivery and extended-release formulations.^{10,25} The development of M₃ receptor-specific anti-muscarinic agents such as darifenacin and zamifenacin^{19,26} holds promise for therapeutic benefit with fewer side effects. Although several industry-funded studies have demonstrated the safety and efficacy of these agents, none have been conducted in subjects with SCI.

Panel recommendation:

Phase I or Phase IIa clinical trials of the safety and efficacy of M₃ receptor-specific anti-muscarinic agents in individuals with SCI.

Electrostimulation of bladder

The panel reviewed two informative research syntheses on electrostimulation of the bladder by Rijkhoff et al²⁷ and by Elkelini and Hassouna.²⁸ These syntheses described the four possible sites where electrical stimulation results in contraction of the detrusor muscle to enable voiding. These sites include the bladder wall, the pelvic nerves, the sacral roots (intradural and extradural) and the spinal cord. Clinical experience, and formal clinical trials, with various techniques were summarized. With over 1000 patients managed worldwide, the Brindley method of sacral nerve stimulation with sacral nerve afferent neurectomy was identified as a useful and effective method for bladder management following SCI. Future research that enables selective detrusor activation without the sacral afferent neurectomy was viewed by the panel as representing an important line of inquiry. Approaches could include selective electrodes on the sacral nerves, genital nerve neuromodulation for bladder inhibition and incontinence management, or blocking the pudendal

nerve with high frequency stimulation or other nerve blocking protocols. Blocking the pudendal nerve would eliminate the high urethral resistance that prevents urination during bladder contractions. There are also important electrical stimulation approaches that do not involve the sacral nerves. Stimulation of the genital nerve alone is being investigated by several groups using conditional (for patients who are aware of the need to void) and intermittent (for patients who are unaware) stimulation as a means to inhibit the bladder and prevent incontinence. Finally, blocking the pudendal nerve with methods just described is an approach that could allow for reflex voiding methods such as suprapubic tapping/hair pulling to result in better bladder emptying.

Techniques to enhance reflex voiding (e.g. botulinum toxin, urethral stents, sphincterotomy and suprapubic tapping) were discussed and their current limitations with respect to DSD, residual volumes, urinary tract infections and autonomic dysreflexia were acknowledged. The prospects of using anal dilation or vibratory stimulation of suprapubic, perineal or penile areas to enhance voiding were considered. The risk of autonomic dysreflexia was identified as a significant concern using these methods. There was consensus that innovative approaches to improve reflex voiding merit clinical trials.

Panel Recommendation:

Late-stage animal or early-stage human clinical trials of sacral nerve electrostimulation coupled with pudendal nerve blocking stimulation to enhance voiding and genital nerve stimulation to reduce urinary incontinence in persons with SCI

Devices, products, strategies and policies for management of incontinence/infection

Development and testing of products for management of incontinence and infection remains largely in the hands of the continence industry. ONF's role with respect to partnerships with industry is to encourage and enable research specifically with the SCI population, recognizing that this population has particular needs that may not be addressed in broader ranging trials with other patient groups with voiding difficulty. In particular, urinary tract infections remain a major burden following SCI and new methods for management of incontinence need to be evaluated for their ability to reduce this major, continuing concern.

The panel reviewed research syntheses on catheter design,²⁹ biomaterials for urinary tract applications³⁰ and urinary catheter policies for long term bladder drainage.³¹ The panel acknowledged the important research currently being undertaken by industry on intermittent catheter design e.g. with respect to the

efficacy and safety of hydrophilic and other coatings,^{29,32} pre-insertion tips and other innovations.^{30,33} Urethral trauma and strictures, and encrustation of catheters, continue to cause significant morbidity³⁴ and alleviation of these complications will likely add appreciably to the quality of life of individuals with voiding dysfunction.

Indwelling catheters e.g. suprapubic and urethral (Foley) catheters, are used by appreciable numbers of patients, oftentimes out of necessity because of inability to use, or failure of, intermittent catheterization. Establishing the relative merits and specific clinical indications for suprapubic versus indwelling urethral Foley catheters constitute important lines of inquiry. Clinical studies on ways to prevent or minimize complications from indwelling catheters are needed.

There has been concern about increased risk of bladder cancer in those with long term indwelling catheters. The published incidence of bladder cancer has varied widely.³⁵⁻³⁸ Adjusting for age-standardized incidence, it has varied from 720/1000,000 to 30/1000,000. In the latter group, this was the same incidence as the general population in the area where the study was conducted.³⁸ There are many possible reasons for these differences. Smaller prospective studies have in their denominator patients who were inpatients or having symptoms, whereas larger retrospective studies have considered the entire population with SCI. Age-adjusted incidences have not always been used, there were no uniform screening procedures, other environmental factors were often not taken into account (such as the smoking pattern of the group studied, the type of catheter used and the material it was made from, and the exposure to environmental toxins).³⁸ The possibility of an increased risk of bladder cancer from an indwelling catheter therefore remains unanswered. Carefully controlled, large-scale, multi-center prospective studies would be expected to help answer this question. Until then, cystoscopic monitoring of individuals with long term indwelling catheters seems prudent. This is particularly important if a person with an indwelling catheter presents with hematuria.³⁹

Intraurethral sphincter prostheses to treat hyporeflexive bladders in women and men were considered to be a potentially useful innovation and worthy of further research. These prostheses, which typically involve a short silicone self-retaining catheter with valve and/or pump, can be activated by a remote control unit. For pump devices, the activator is placed over the lower abdomen and a press button used to energize the pump by magnetic coupling. Once activated the pump rotates at high speed drawing urine from the bladder.^{40,41} Valved devices rely on passive

abdominal pressure on bladder contraction for urination when the valve is open. The prosthesis can remain in the bladder for several weeks and provide an alternative to clean intermittent catheterization. Several published reports attest to the potential utility of the devices, however concerns in otherwise healthy females include discomfort, irritation, leakage, mucus clots, uninhibited detrusor contractions and technical dysfunction.⁴⁰⁻⁴⁴ The longer urethra of males may make it more difficult to place and remove these devices. With the lack of urethral sensations for many persons with SCI, discomfort would be expected to be less of a problem, however one may not be aware of irritation or migration of the device. Clearly further testing and product development will be important prior to the implants gaining widespread clinical application.

External collection devices in general, and for women in particular, remain problematic and innovations in this area are to be encouraged. Novel or hybrid collection devices are currently being developed (e.g. Self-Cath Hydrogel by Mentor, or Daisy by Medexus Uro. Inc for male incontinence). Clinical trials of these devices in individuals with SCI would be helpful to establish the usefulness of these products for this patient population.

Panel were informed by the Cochrane review on urinary catheter policies for long-term bladder drainage³¹ and articles concerning issues of meatal hygiene, personal washing and frequent catheter changes.^{34,45} The observations that improving personal hygiene just by itself does not reduce catheter-associated bacteriuria was brought to the attention of the panel.⁴⁵

Panel Recommendations:

- 1) *Early stage (Phase I or Phase IIa) clinical trials of safety and efficacy of intra-urethral valve catheters in persons with SCI with possible partnerships with industry*
- 2) *Development and testing of novel external collection devices, with high priority been given to devices for women.*

Management of urinary tract infection

The panel considered management of UTI in three areas: pharmacology, antimicrobial prophylaxis and bacterial interference. Reviews by Biering-Sorensen et al⁴⁶ and Morton et al⁴⁷ provided necessary context, as did the Consensus Statement from the National Institute on Disability and Rehabilitation⁴⁸ and a meta-analysis conducted for the Agency for Health Care Policy and Research.⁴⁹ It was evident that the pharmaceutical industry drives the agenda on research and development of new pharmacotherapeutics and that the costs of large scale clinical trials to establish safety and efficacy fall outside the scope of a publicly funded organization like

ONF. The panel therefore focused attention on the issues of prophylaxis and bacterial interference.

Antimicrobial prophylaxis does not appear to decrease symptomatic infections but does reduce asymptomatic bacteriuria among acute patients.⁴⁷ Prophylaxis results in an approximately twofold increase in antimicrobial-resistant bacteria. In light of these observations the panel considered that alternative approaches to management of infection that circumvent the problem of uropathogen resistance to anti-microbials may prove a profitable line of inquiry.

Bacterial interference i.e. using certain avirulent bacteria ("probiotics") to prevent or reduce colonization by uropathogens is emerging as a novel approach to the dual problems of infection and pathogen resistance to anti-microbials.^{50,51} Intentional bladder colonization with benign organisms, to date, has proceeded along two lines: use of *E. coli* strains as a protective interfering strategy,^{52,53} and use of various strains of *lactobacillus* to treat infection.^{50,51} Evidence of the efficacy of both approaches is accumulating, but not definitive, and more research is needed to thoroughly explore the potential of these novel strategies for management of UTI.

Panel recommendation:

Early stage clinical trials of the safety and efficacy of probiotics in individuals with SCI either for prophylaxis or as adjunctive therapy, with outcome assessment in one or more of: tolerability, inflammation, bacteriuria, treatable infection.

Medical and surgical interventions

Surgical approaches to the problems of voiding dysfunction following SCI have been reviewed by Gray and Yang.⁵⁴ Conventional procedures include external sphincterotomy (to reduce outlet resistance), permanent or temporary intraurethral stents (helpful in cases of urethral strictures or prostatic obstruction), indwelling suprapubic catheters (for patients who experience difficulty with catheter exchange, have chronic urethritis or epididymitis, or who are sexually active), bladder augmentation (to increase bladder capacity), urinary diversion such as the ileal conduit and continent diversions e.g. orthotopic or catheterizable (via abdominal stoma) pouches. Many technical variants of each surgery have been reported and each procedure has recognized advantages and disadvantages. More innovative or experimental surgical case reports include replacing the detrusor with innervated muscle flaps (e.g. latissimus dorsi or rectus abdominus).^{55,56} Stem-cell derived bladder tissue for augmentation, bladder replacement, or other applications, all represent future possibilities.⁵⁷⁻⁵⁹

The panel recognized the reluctance of many persons with SCI to have irreversible procedures in light of the current optimism surrounding restorative therapeutic approaches to SCI.⁶⁰ One clinically useful area of future research would be identification of the optimal patient selection criteria (decision trees or treatment algorithms) for each of the procedures.

The etiology, pathophysiology and the prevention and management of bladder stone disease were all identified by the panel as being clinically important and deserving of further inquiry.⁶¹ Prevention of catheter encrustation (stone formation) would potentially reduce catheter blockage and autonomic dysreflexia. A better understanding of the etiology and pathophysiology of catheter encrustation is needed. This would also be expected to help find ways to prevent kidney and ureteral stones. Conventional surgical and nonsurgical treatment for stones should be adapted for the specific clinical presentation of persons with SCI. Treatment options have been reviewed by Bodner and Perkas⁶² and include cystoscopy and cystolitholapaxy for bladder stones, laser uteroscopy and lithotripsy for ureteral stones, and extracorporeal shock-wave lithotripsy or percutaneous nephrostolithotomy for renal stones.

Panel recommendation:

Clinical trials of innovative approaches to prevention, or the medical or surgical management, of stone disease in persons with SCI

Conclusion

Despite advances in many aspects of urological care, voiding dysfunction and its various sequelae continue to compromise the quality of life of individuals sustaining SCI. Urological concerns also represent a substantial burden on the Canadian health care system by virtue of the demand on primary care, specialist consults and emergency departments. Clearly innovation is required in the areas of prevention, catheter design, and medical and surgical management to address the many and various problems and to inform clinical best practices. The priorities identified here represent an attempt to guide future research along lines that are considered viable, innovative and responsive to the specific needs of people with SCI. Potential benefits to other patient populations may be a welcome offshoot of this undertaking. □

Ontario Neurotrauma Foundation International Panel of Experts

Name	Position/Affiliation	Expertise
K. C. Hayes, PhD	Dept of PM&R, Univ Western Ontario	Panel Chair, Chair of ONF SCI Quality of Life Committee
T. Linsenmeyer, MD	Professor, Dept of PM&R, New Jersey Medical School Director of Urology, Kessler Med Rehab Center	Internationally recognized authority on Urological issues in SCI
K. D. Ethans, MD, FRCPC	Assistant Professor, Depts of Internal Medicine and PM&R, Univ Manitoba	Director of Spinal Cord Unit
K. N. Moore, RN, PhD	Associate Professor, School of Nursing, Univ Alberta	Cochrane Incontinence Group
J. S. Walter, PhD	Adjunct Associate Professor, Urology, Loyola Univ of Chicago, Illinois	Director of Autonomic Dysfunction Laboratory
H. Razvi, MD, FRCSC	Associate Professor, Division Chair of Urology, Univ Western Ontario	Urinary Stone Disease
G. Reid, PhD	Professor, Dept Microbiology & Immunology, Univ Western Ontario Director, Canadian Research and Development Centre for Probiotics, Univ Western Ontario	Microbiology & Probiotics
J. W. L. Wilson, MD, FRCSC	Associate Professor, Queens Univ Head of Dept of Urology,	Surgical Urology
R. Das, BSc MBA	Consumer with SCI	Board Member, Rick Hansen SCI Alliance
C. Kagan, BA	Ontario Neurotrauma Foundation	Funding Program Coordinator
J. L. K.Kramer, BSc	Neuroscience Program, Univ Western Ontario	Technical Resource
K. Bassett-Spiers	Ontario Neurotrauma Foundation	Executive Director

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