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BPS/INTERSTITIAL CYSTITIS (D CASTRO-DIAZ AND Y IGAWA, SECTION EDITORS)

Role of Surgery in Bladder Pain Syndrome

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Abstract

Purpose of Review Bladder pain syndrome is a clinical condition with many aspects to its presentation and numerous suggested treatments, many of which remain controversial. Reconstructive surgery should only be considered when all the conservative options have been exhausted and only after careful counselling. The purpose of this review is to demonstrate the current evidence in the surgical management of this disease, preparatory to which we have reviewed the surgical aspects.

Recent Findings For medical treatment, the evidence base is of poor quality and based on case series. Nevertheless, in carefully selected patients after appropriate counselling, excellent results can be achieved both with total cystectomy and augmentation cystoplasty or a continent or incontinent diversion.

Summary We reviewed the various success rates of the treatments which are described. A multidisciplinary approach is essential to a successful outcome, and it is essential to consider not only the urological, but also broader medical and psychological consequences seen with bladder pain syndrome. Further research should focus on clearly categorizing the patients with well-defined clinical criteria to provide high-quality evidence to support the selection of the most effective treatment.

Keywords Bladder pain syndrome (BPS) · Interstitial cystitis (IC) · IC/BPS · Diversion · Neobladder · Continent/incontinent diversion · Cystectomy

Introduction

Lower urinary tract symptoms (LUTS) are non-specific in terms of aetiology. Bladder pain syndrome (BPS), otherwise known as painful bladder syndrome/interstitial cystitis, is a non-specific symptom complex characterized by persistent or recurrent pain in the suprapubic or perineal area which is thought to be arising in the bladder. The principal symptom of pain is the trigger for urinary frequency as voiding provides temporary relief of the pain. Understandably, the pelvic pain complex is associated with other symptoms such as dyspareunia. There is a whole spectrum of presentation from relatively mild forms of this symptom complex to cases where voiding is occurring every 15 min. Clearly, although this is not a life-threatening disease, it produces enormous disruption of quality of life and is often difficult to manage [1••].

The ICS define BPS as "the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology [2••]. It is estimated that it can affect up to 300 per 100,000 women with a 10:1 female predominance [3••]. The European Society for the Study of Interstitial Cystitis (ESSIC) use the term "bladder pain syndrome" defined as "chronic pelvic pain, pressure or discomfort perceived to be related to the urinary bladder, with at least one other urinary symptom such as the persistent urge to void or urinary frequency" [4••].

The specific aetiology of BPS remains an enigma. It is believed to be the consequence of a multifactorial disease spectrum with many proposed aetiologies [5•] (Fig. 1). A prominent theory is that an infectious cause could be the cause of the disease but many have investigated this theory and failed to prove it [6•]. However, supportive evidence is provided by the finding that urinary infections are more frequent in BPS patients during childhood and adolescence [7•]. There is an evidence that up to (36%) of women with

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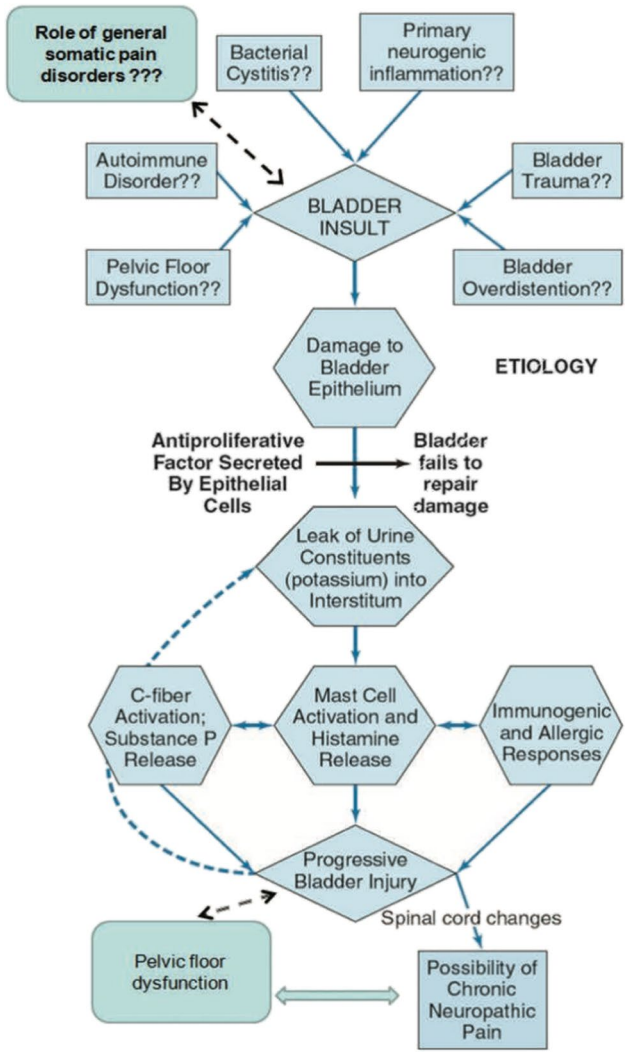

Fig. 1 Adopted from Committee on Bladder Pain Syndrome. Fifth International Consultation on Incontinence. Paris, France; 2012

BPS have evidence of acute urinary tract infection (UTI) apparently triggering chronic BPS [8•]. In 1991, Parson suggested that an abnormality in the bladder epithelial glycosaminoglycan (GAG) layer overlying the urothelium produces the dysfunction in BPS patients [9•]. Tight junction proteins, E-cadherin, and zonula occludens-1 have also been found to be downregulated in bladder pain syndrome patients [10•]. These changes can increase the epithelial permeability which can expose the sub-epithelial afferent nerve endings to urinary stimuli [11•]. Mast cell (MC) activation as an important factor in the pathogenesis of the BPS was postulated by Simmons in 1961 [12]. Since then, MC activation has been believed to be a pathognomonic histological marker in BPS. However, emerging evidence suggests that it might not be a specific feature of BPS and it could be a common pathological pathway for lower urinary tract diseases [13•, 14•].

Table 1 ESSIC classification of BPS based of cystoscopy with hydrodistension and biopsy [4••]

	Cystoscopy with hydrodistension			
	Not done	Normal	Glomerulations[a]	Hunner's lesion[b]
Biopsy				
Not done	XX	1X	2X	3X
Normal	XA	1A	2A	3A
Inconclusive	XB	1B	2B	3B
Positive[c]	XC	1C	2C	3C

[a]Cystoscopy: glomerulation grade 2–3

[b]Lesion per Fall's definition with/without glomerulations

[c]Histology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis

The diagnosis of BPS is usually made by application of the definition and clinically excluding any confusable diseases. NIDDK criteria, which were formulated more than 30 years ago, were intended to provide a logical basis for the standardization of scientific studies. It is however now recognized that the strict application of these criteria may fail to diagnose 60% of the patients with BPS [4••, 15•]. Bladder pain during filling is the pathognomonic symptom with associated storage symptoms and pelvic pain leading to symptoms such as dyspareunia in women and painful ejaculation in men. This is quite distinct to compelling desire to pass urine for fear of leakage which is the characteristic of the urgency seen with overactive bladder symptom complex. Patient must therefore be carefully assessed clinically to ensure that other disorders (confusable diseases) that can cause pelvic pain are ruled out. Investigations are aimed at excluding urinary tract infections or any other intravesical pathologies. The ESSIC has proposed a standardized scheme based on cystoscopy findings and biopsy results on the basis of which BPS patients can be further categorized (Table 1) [4••].

Current consensus emphasizes the importance of performing a cystoscopy with hydrodistension under a light general anaesthetic, using 1-m gravity elevation over the patient for the fluid infusion bag. Classically, the appearances are those of significant post-distension reddening and bleeding, associated with a rise in pulse and blood pressure. By themselves, bladder glomerulations are not considered specific for the disease [16]. The diagnostic value in patients with a lower bladder capacity, generally less than 400 ml may indicate a bladder-centric disease rather than a systemic one [17]. Even though it is common to use hydrodistension to identify patients with Hunner's ulcers. Recent data suggest that patients with Hunner's lesions may have a clinically and pathologically different disease from patients without

lesions [18, 19, 20••]. A major issue though to highlight is the disparity in defining what represents a Hunner's ulcer. These lesions may vary from a significant split of the bladder lining up towards the bladder dome in a patient with a very fibrotic bladder of reduced abnormality capacity to areas of ulceration manifesting after cystodistension. This is an issue which needs to be clarified in future research in this area. Clearly, in current practice, there is a considerable variability in the diagnosis and management of bladder pain syndrome [21].

Having made a diagnosis of bladder pain syndrome, the management is empirical. The evidence behind most BPS treatments is of poor quality [22]. Treatments are considered in a hierarchical fashion (Table 2).

Here is a table summarizing the common oral and intravesical installation agents with the grade and level of recommendations (Table 3).

Minimal Invasive Therapy

Cystoscopy and Cystodistension

Since its description in 1922, cystodistension has been used in the treatment for BPS. Even though there is great variability in the technique used, it is usually performed under light general anaesthesia, with the irrigation pressure of 100 cm H2O for 2–3 min (Fig. 2). Post-distension, the mucosa should be inspected for any possible tears to avoid bladder perforation [24]. It is important never to biopsy the bladder particularly in women before performing a cystodistension. Even though there are some data showing short lasting symptomatic improvement, there is no strong evidence behind cystodistension in the context of treatment and it is recommended to be only used as a diagnostic tool [22, 25]. In our experience, we certainly see benefit from this procedure in nearly 50% of patients although the duration of efficacy is very variable. We also as a routine carry out

Table 2 stepwise treatment approach for bladder pain syndrome [23]

First-line treatments
-General relaxation/stress management
-Patient education
-Self-care/behaviour modification
-Pain management
Second-line treatments
-Specialized manual physical therapy
-Oral agents: amitriptyline, hydroxyzine, cimetidine, PPS
-Intravesical therapy: DMSO, heparin, lidocaine
-Pain management
Third-line treatments
-Cystoscopy under anaesthesia with hydrodistension
-Treatment of Hunner's lesions, if found
-Pain management
Fourth-line treatments
-Intradetrusor botulinum A toxin
-Neuromodulation
-Pain management
Fifth-line treatments
-Cyclosporine A
-Pain management
Sixth-line treatments
-Urinary diversion (with or without cystectomy)
-Substitution cystoplasty
-Pain management

Table 3 *The FDA have issued a warning of possible pigmentary maculopathy with long term use. From the Committee on Bladder Pain Syndrome. Fifth International Consultation on Incontinence. Paris, France; 2012

Treatment	ICI	EAU	Giannantoni
Oral therapies			
Amitriptyline	B: 2	A: 1	A: 1
Analgesics	C: 4	C: 2	
Hydroxyzine	D: 1	A: 1	
PPS*	D: 1	A: 1	C: 1
Cyclosporine	C: 3	A: 1	A: 1
L-Arginine	– A: 1		A: 1
Antibiotic regimens	D: 4		
Azathioprine	D: 4		
Benzydamine	D: 3		
Chloroquine derivatives	D: 4		
Cimetidine	C: 3		
Doxycycline	D: 4		
Duloxetine	– C: 4		
Gabapentin	C: 4		
Methotrexate	D: 4		
Misoprostol	D: 4		
Montelukast	D: 4		
Nalmefene	– A: 1		
Nifedipine	D: 4		
Quercetin	D: 4		
Tanezumab	D: 1		
Suplatast tosilate	D: 3		
Vitamin E	D: 4		
Intravesical therapies			
Lidocaine	C: 2		
DMSO	B: 2	A: 1	
Heparin	C: 3		
Hyaluronic acid	D: 1	B: 2	
Chondroitin sulphate	D: 4	B: 2	A: 1
PPS	D: 4	A: 1	
Oxybutynin	D: 4		
BTX (intramural)	A: 1		A: 1

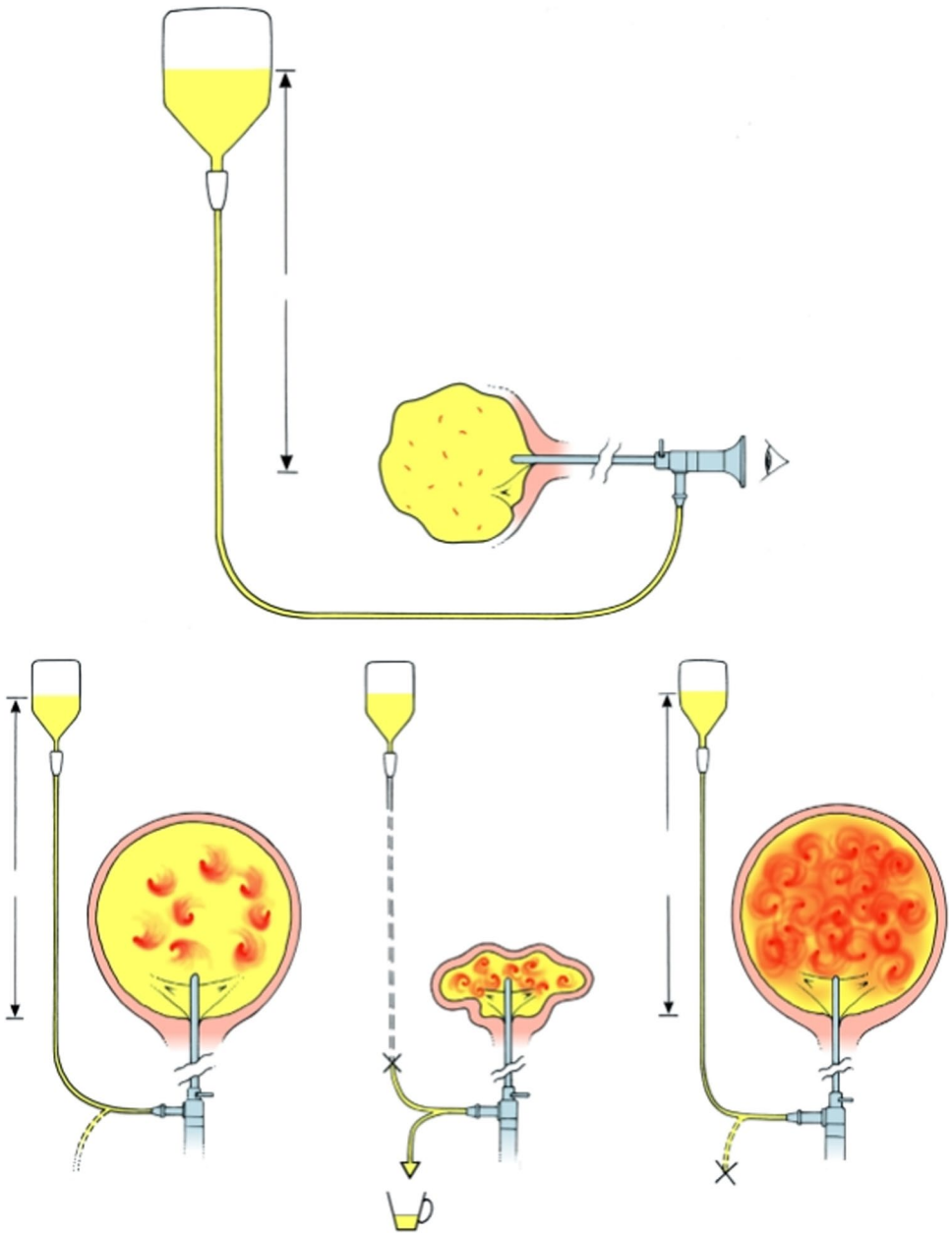

Fig. 2 Cystodistension under light general anaesthesia. Copyright C.R. Chapple

a urethral calibration to 35F at the time of cystodistension. An important aspect of a cystodistension as noted above is to record the anatomical capacity of the bladder as lower capacities have a poorer prognosis and are more likely to progress to major reconstructive surgery.

Botulinum Toxin A (Onabotulinum Toxin) Injection

If the previous treatments did not produce satisfactory symptom improvement, botulinum toxin A (BTX) injection can be offered.

In 2004, Smith et al. reported injecting BTX intravesically and showed positive results with BPS patients which suggested that it may have an anti-nociceptive effect on bladder afferent pathways [26]. Several reports have investigated injecting BTX in BPS patients. Kue investigated injecting BTX followed by hydrodistension. The BTX groups showed a statistically significant improvement in pain scores and bladder capacity compared to hydrodistention alone. It was reported that 200 U had a much higher rate of side effects compared to 100 U with similar effects [27•]. It was shown that at 8 weeks, there is a statistical improvement in pain scores after BTX injection compared to placebo in addition to an increase in functional bladder capacity. This

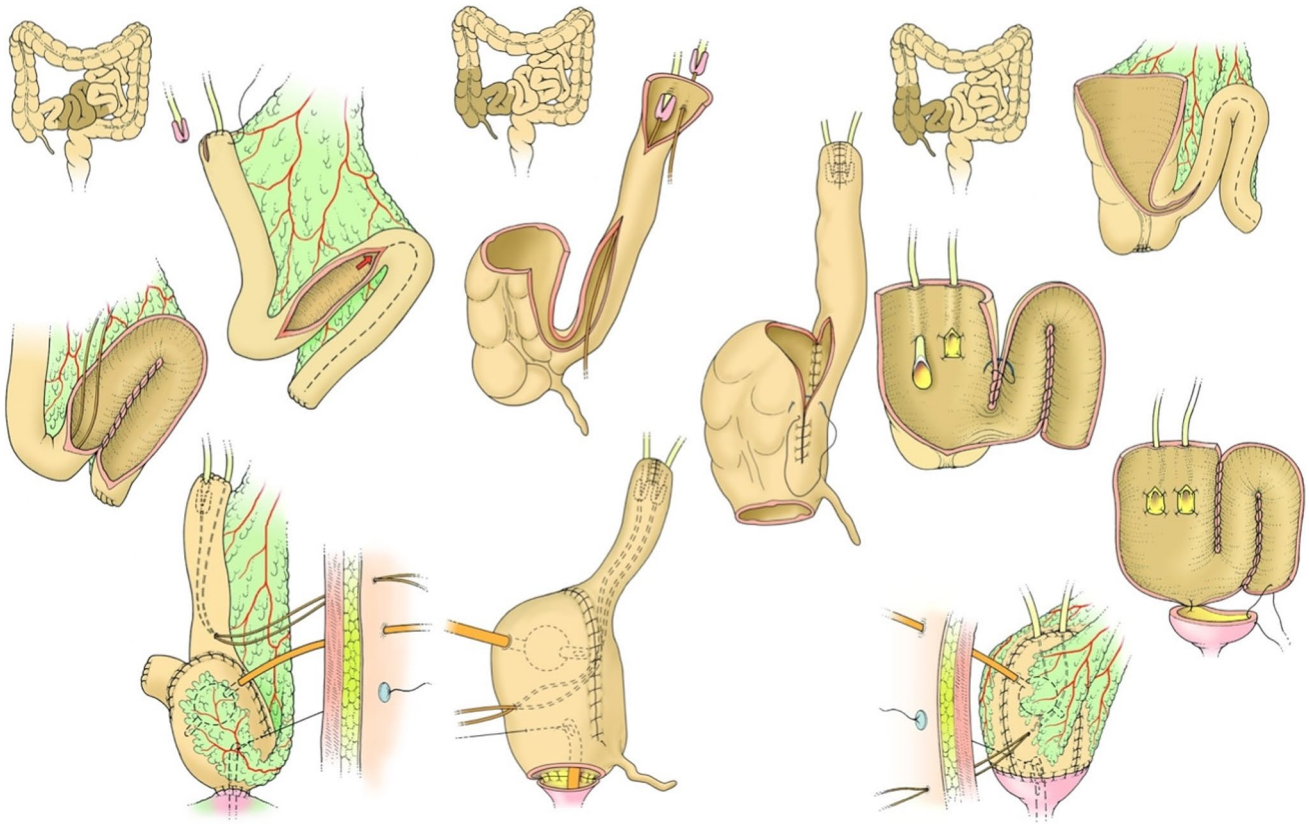

Fig. 3 Various techniques of neobladder formation. Copyright C.R. Chapple

study has only included patient with non-ulcerative BPS [28]. Usually, BTX injection is limited to non-ulcer BPS as several reports have found that ulcer type might not respond well to BTX injection [29]. However, other groups have investigated injecting BTX to the trigone and the results were comparable between ulcer and non-ulcer BPS patients [30]. It is strongly recommended to consider BTX injection therapy in addition to cystodistension if the intravesical installations failed [22].

Transurethral Resection of Hunner's Lesion

In patients with identified Hunner's ulcer, many minimal invasive procedures were proposed including resection, electrocoagulation, and laser ablation [31]. Several reports have suggested that these treatments of a Hunner's lesion can provide some symptomatic relieve which last up to an average of 23 months compared to just hydrodistension alone which lasted an average of 4 months [32]. Laser ablation of Hunner's ulcers showed a clinically significant improvement in pain scores, urgency, nocturia, and frequency with half of the patients having a persistent improvement for a mean of 19 months. The remainder of the patient has required one or more interventions and their improvement was for a shorter period of time [33]. It is strongly recommended to consider transurethral resection or ablative therapy to patient with Hunner's lesion [22]. As noted above, the major criticism of this work remains the debate over what represents a Hunner's ulcer and the lack of standardization between reports.

Major Surgical Intervention

After failure of the other modalities, major reconstructive surgery can be offered. But this should be reserved for a small subset of patients with severe symptoms refractory to conventional therapy as a complete symptomatic resolution might not always be achieved. Even though BPS is not a life-threatening disease, it is a debilitating disease and can highly impact the quality of life. Therefore, we have to intervene weighing the risks and the benefits [34]. Assuming the bladder to be the central cause of symptoms, major reconstructive surgery aims to remove it or divert urine from it [35]. It is strongly recommended not to proceed to surgical intervention until other measures fail [22]. Furthermore, we would emphasize the importance of careful consideration of the major psychological issues that often present no doubt related to the enormous disruption of the patient's quality

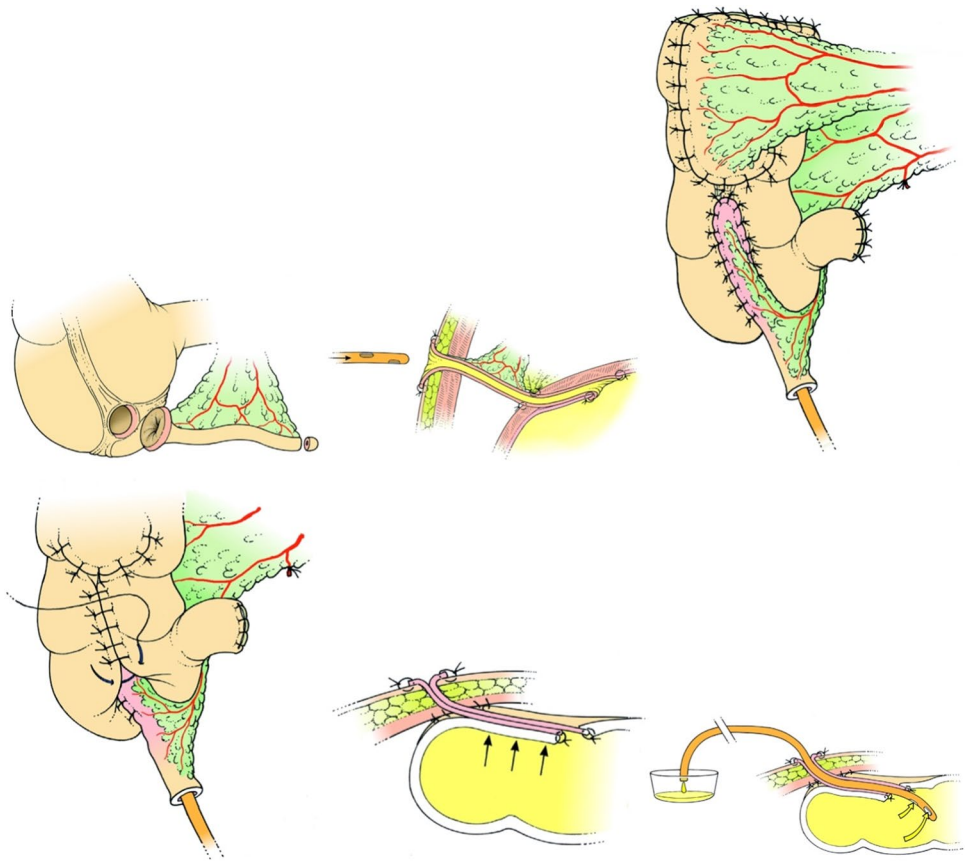

Fig. 4 The Mitrofanoff appendix conduit procedure. Copyright C.R. Chapple

of life because of the urinary frequency both day and night, and the associated pain and dyspareunia which have been resistant to all medical and minimally invasive treatment modalities. It is only after detailed multidisciplinary review and counselling of the consequences of such surgery that we proceed to such treatment. We believe that this approach leads to the optimal outcomes in this severely debilitated group of patients [36••].

Supra-trigonal cystectomy with substitution cystoplasty: Using this approach, the bladder is resected down to the trigone, leaving a 1-cm margin around it for the bowel segment to be anastomosed to. This is the most favourable surgical option to preserve continence, and it provides a good chance of spontaneous voiding (12.5% required ISC) and the advantage of not requiring to re-implant the ureters [37]. However, patients must be counselled about the need to self-catheterize. It has been reported that the rate of symptomatic improvement is up to 73.4% [36••].
Sub-trigonal cystectomy with neobladder formation:

In this technique, we excise the bladder down but not including the bladder neck as this will include re-implanting the ureters. Trigonal disease is reported in about 50% of patients and some authors have suggested that it could be the cause of the surgical failure if it was left in [38] The overall symptomatic improvement is up to 94.9% which is the highest success rate compared to other major surgical techniques [36••]. This approach is associated with high chance of voiding dysfunction so the patient should be able to perform self-catheterization as it reported that more than 40% of patients might need it [39]. In all these patients, careful preoperative counselling is mandatory, relating to the need for ISC (Fig. 3).

Cystectomy with Continent Diversion with Mitrofanoff

Performing a simple cystectomy and a continent urinary diversion with Mitrofanoff has been reported by some

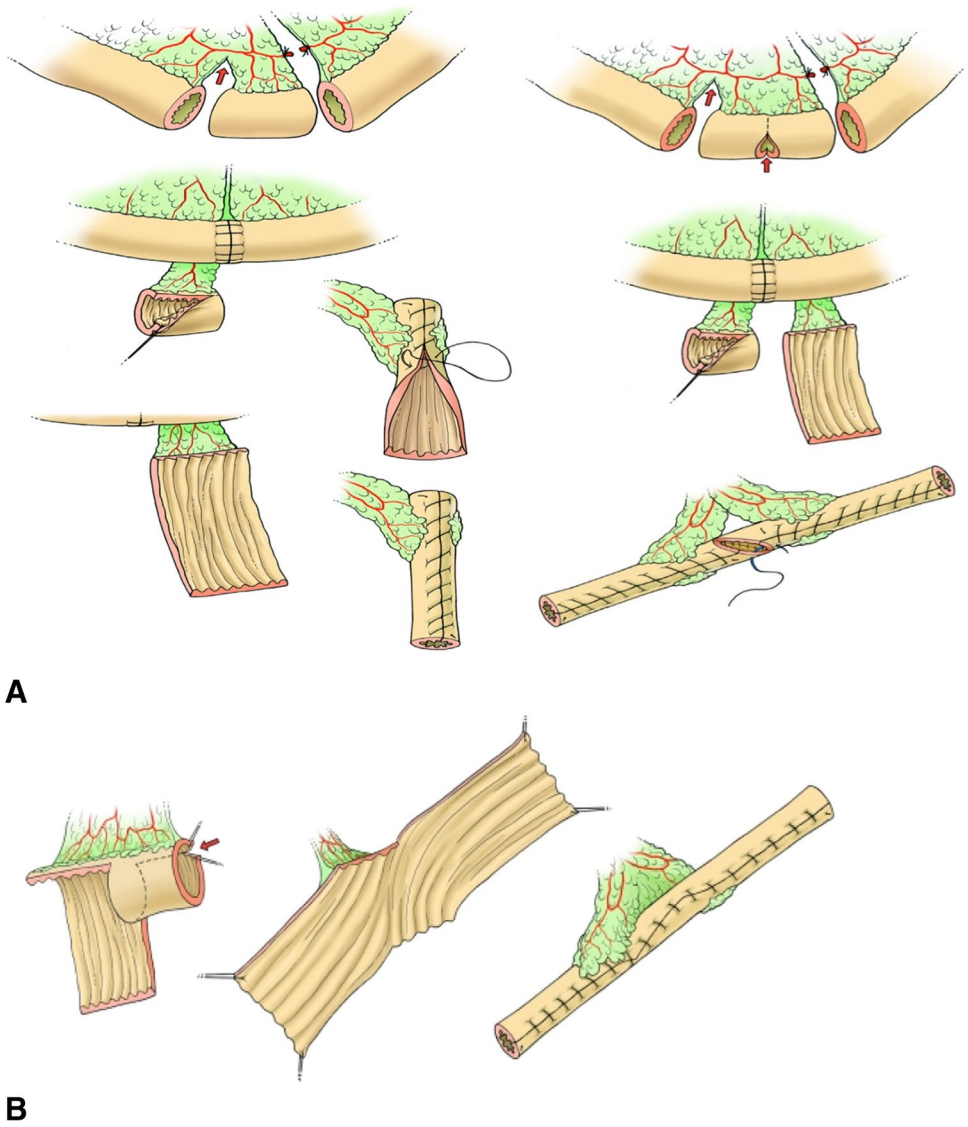

Fig. 5 Copyright C.R. Chapple. **A** fashioning the ileal catheterizable tube. **B** The remodeling modification for the ileal tube, which we favour

authors (Fig. 4). Downey reported five cases which underwent this procedure. Unfortunately, two of those patients had persistent pain on follow-up and the neobladder had to be excised and form an ileal conduit [40].

In many cases, an appendix of adequate calibre is not available. In this circumstance, the formation of an ileal substitute for the appendix is fashioned (Fig. 5).

Urinary diversion without cystectomy:

Incontinent urinary diversion has been advocated without performing cystectomy, eliminating the distention of the bladder and urine contact with the bladder mucosa. Some authors have advocated performing a urinary diversion without cystectomy being a less morbid procedure and the fact that some patients do get a positive result without significant adverse effects [35, 41]. We have major concerns regarding the retained bladder which in our experience leads on to residual symptoms of incomplete emptying and residual pain and in many cases pyocystis [42]. In our experience, in most patients in the longer term, this has led onto a secondary cystectomy, Indeed, Osman et al. reported a 63.40% overall symptom improvement in patient undergoing urinary diversion alone. Clearly, it has a lower symptom improvement rate compared to other surgical procedures [36••].

Urinary diversion with cystectomy:

Although cystectomy with ileal conduit is often performed as a secondary procedure when the patient has

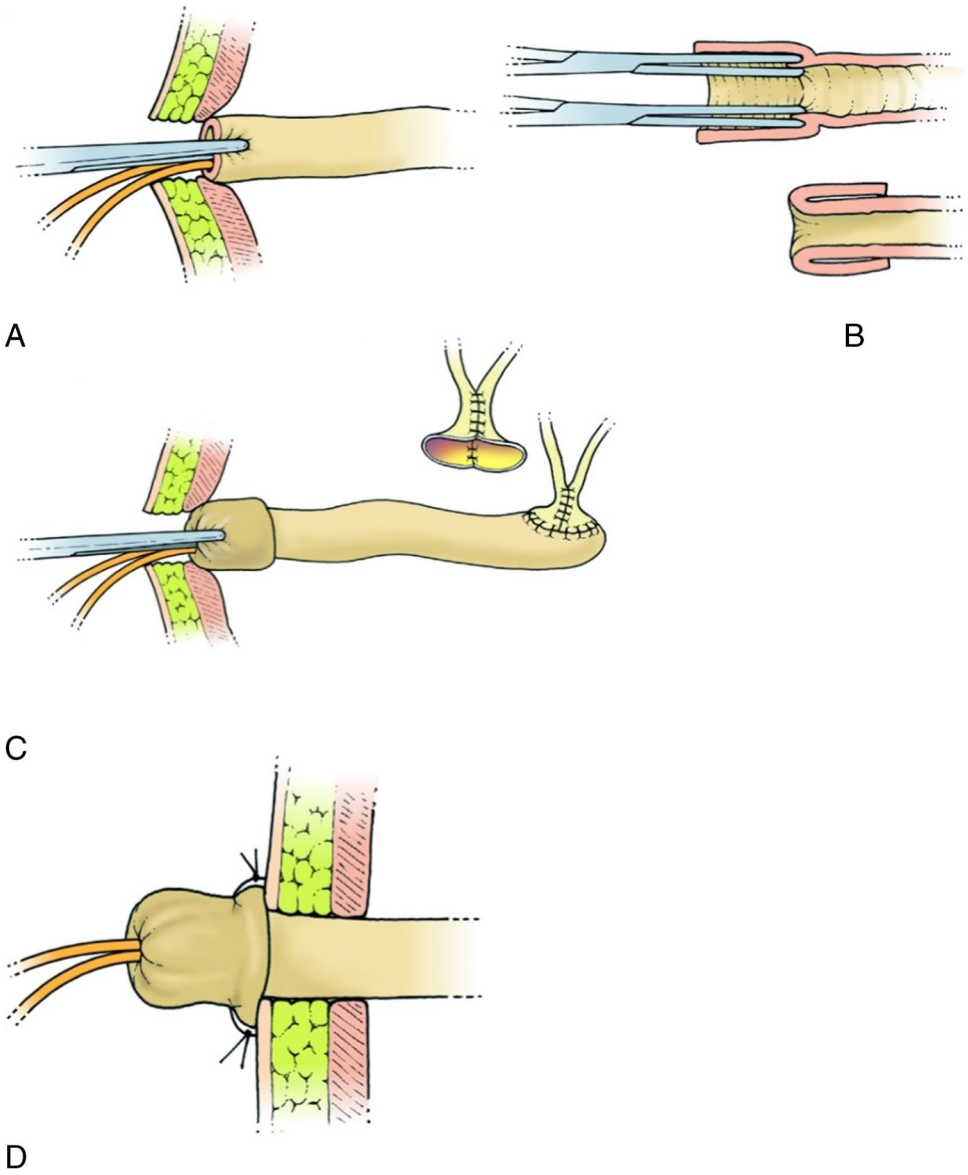

Fig. 6 Ileal conduit. Copyright C.R. Chapple. **A** Pulling the conduit through the abdominal wall. **B/C** Inverting the distal bowel first before pulling through (our preferred approach). **D** The final nipple

had a failed subtotal cystectomy or urinary diversion, in our experience, this may be the case in a proportion of our patients who have undergone a continent diversion. It can, however, be performed primarily, and it has been reported to be performed as a primary procedure in about 11% of patients undergoing major surgical reconstruction, and the overall symptomatic improvement is reported to be 82% [22, 36••]. Our experience is that we have obtained very satisfactory results based on patient's feedback in performing this in a larger proportion of our patients following careful counselling [40] (Fig. 6).

Conclusion

Major surgical reconstruction is an option for BPS patients with severe symptoms after failure of other modalities. Careful patient selection and education is essential knowing the risks and the chance of persistent pain after such irreversible major procedure.

Future research may help an evidence-guided intervention that is tailored to each different BPS subtype.

Declarations

Conflict of Interest The authors declare no competing interests.

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