Guidelines on
Chronic Pelvic Pain

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5. CHRONIC PELVIC PAIN

5.1 Background

5.1.1 Introduction

Pain management is a subject afflicted by failure to identify its pathophysiological origins. The problem is most commonly experienced as 'interstitial cystitis (IC)' or 'chronic prostatitis (CP)'. These terms reflect the clinical interpretation of the symptoms described by patients. Intuitively, inflammation is identified as the chief suspect because the symptoms suggest it. Applying the syllable 'itis' as a suffix seems reasonable given the confidence in the eventual discovery of evidence of a cause.

Current attitudes reflect the popularity of the 'verification' principle in clinical science. This is predicated by the question "What would lead me to stand by my hypothesis?". In contradistinction, 'falsification', advocated by Karl Popper, questions "What would lead me to believe that my hypothesis be wrong?". Verification makes it easy to use an inflammatory label before evidence has been procured.

The conditions discussed here are diagnosed contingent on failure to identify any manifestation of a known pathology. This does not preclude the subsequent discovery of a hitherto unrecognized pathological process; current methods of investigation may be too crude.

Thus the terminology used is confusing, but it results from an approach to science that, while waning, was nevertheless respectable. The American pragmatist philosophers asserted that a theory was true if it worked. Nowadays, we see that the theories addressing chronic pelvic pain have ceased to work and a re-evaluation is required, along with an adjustment of the terminology. Nevertheless, if clinicians are to participate in this process, clarity dictates that the old, familiar terminology should be included in the descriptions.

The fact that a group of genuine disease entities is being addressed is supported by the common currency of the symptom complexes that are described by disparate people from many different nations. That a multinational group of Europeans can come together in consensus over such an enigmatic subject hints at tangibility, even if it has yet to be realized.

5.2 Definitions of chronic pelvic pain and terminology

Chronic pelvic pain

Chronic pelvic pain is non-malignant pain perceived in structures related to the pelvis of either men or women. In the case of documented nociceptive pain that becomes chronic, the pain must have been continuous or recurrent for at least 6 months. If non-acute pain mechanisms are documented then the pain may be regarded as chronic, irrespective of the time period. In all cases, there may be associated negative cognitive, behavioural and social consequences (new definition).

The suffixes 'algia' and 'dynia' are frequently used as a means of providing a patient with a tangible diagnosis, which in itself may be a therapeutic contribution. However, in these guidelines, we have elected for the sake of clarity to avoid these terms. Our definitions are in line with the most recent recommendation for terminology laid down by the International Continence Society (ICS) (1) and use the axial structure of the International Association for the Study of Pain (IASP) classification (see Table 1) (2).

Pelvic pain syndrome (CPPS) is the occurrence of persistent or recurrent episodic pelvic pain associated with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. There is no proven infection or other obvious pathology (adopted from ICS 2002) (1).

Bladder pain syndrome is 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 (ICS 2002) (1).

Urethral pain syndrome is the occurrence of recurrent episodic urethral pain usually on voiding, with daytime frequency and nocturia, in the absence of proven infection or other obvious pathology (ICS 2002) (1).

Penile pain syndrome is the occurrence of pain within the penis that is not primarily in the urethra, with the absence of proven infection or other obvious pathology (new definition).

Prostate pain syndrome is the occurrence of persistent or recurrent episodic prostate pain, which is associated with symptoms suggestive of urinary tract and/or sexual dysfunction. There is no proven infection or other obvious pathology (new definition).

The definition of prostate pain syndrome has been adapted from the National Institutes of Health (NIH) consensus definition and classification of prostatitis (3) and includes those conditions that they term 'chronic

pelvic pain syndrome'. Using their classification system, prostate pain syndrome may be further subdivided into type A inflammatory and type B non-inflammatory.

Scrotal pain syndrome is the occurrence of persistent or recurrent episodic scrotal pain that is associated with symptoms suggestive of urinary tract or sexual dysfunction. There is no proven epididymo-orchitis or other obvious pathology (ICS 2002) (1).

Testicular pain syndrome is the occurrence of persistent or recurrent episodic pain localized to the testis on examination that is associated with symptoms suggestive of urinary tract or sexual dysfunction. There is no proven epididymo-orchitis or other obvious pathology (new and more specific definition than scrotal pain syndrome).

Post-vasectomy pain syndrome is a scrotal pain syndrome that follows vasectomy (new definition).

Epididymal pain syndrome is the occurrence of persistent or recurrent episodic pain localized to the epididymis on examination that is associated with symptoms suggestive of urinary tract or sexual dysfunction. There is no proven epididymo-orchitis or other obvious pathology (new and more specific definition than scrotal pain syndrome).

Endometriosis-associated pain syndrome is chronic or recurrent pelvic pain where endometriosis is present but does not fully explain all the symptoms (new definition).

Vaginal pain syndrome is the occurrence of persistent or recurrent episodic vaginal pain that is associated with symptoms suggestive of urinary tract or sexual dysfunction. There is no proven vaginal infection or other obvious pathology (ICS 2002).

Vulvar pain syndrome is the occurrence of persistent or recurrent episodic vulvar pain that is either related to the micturition cycle or associated with symptoms suggestive of urinary tract or sexual dysfunction. There is no proven infection or other obvious pathology (ICS 2002) (1).

Generalized vulvar pain syndrome (formally dysaesthetic vulvodynia) refers to vulval burning or pain that cannot be consistently and tightly localized by point-pressure 'mapping' by probing with a cotton-tipped applicator or similar instrument. The vulval vestibule may be involved but the discomfort is not limited to the vestibule. Clinically, the pain may occur with or without provocation (touch, pressure or friction) (International Society for the Study of Vulvovaginal Disease [ISSVD] 1999).

Localized vulvar pain syndrome refers to pain that can be consistently and tightly localized by point-pressure mapping to one or more portions of the vulva. Clinically, the pain usually occurs as a result of provocation (touch, pressure or friction) (ISSVD 1999).

Vestibular pain syndrome (formerly vulval vestibulitis) refers to pain that can be localized by point-pressure mapping to one or more portions of the vulval vestibule.

Clitoral pain syndrome refers to pain that can be localized by point-pressure mapping to the clitoris.

Proctalgia fugax refers to severe, brief, episodic pain that seems to arise in the rectum and occurs at irregular intervals (IASP 1994,(2)).

Anorectal pain syndrome is the occurrence of persistent or recurrent, episodic rectal pain with associated rectal trigger points/tenderness that is related to symptoms of bowel dysfunction. There is no proven infection or other obvious pathology (new definition).

Anismus is the occurrence of anal pain related to the process of defaecation and caused by the failure of the striated pelvic floor musculature, including the external anal sphincter, to relax (new definition).

Pudendal pain syndrome is a neuropathic-type pain arising in the distribution of the pudendal nerve with symptoms and signs of rectal, urinary tract or sexual dysfunction. There is no proven obvious pathology.

Perineal pain syndrome is the occurrence of persistent or recurrent, episodic, perineal pain that is either related to the micturition cycle or associated with symptoms suggestive of urinary tract or sexual dysfunction. There is no proven infection or other obvious pathology (ICS 2002 (1)).

Pelvic floor muscle pain syndrome is the occurrence of persistent or recurrent, episodic, pelvic floor pain with associated trigger points that is either related to the micturition cycle or associated with symptoms suggestive of urinary tract or sexual dysfunction. There is no proven infection or other obvious pathology (new definition).

5.3 Classification of chronic pelvic pain syndromes

Table 1: Classification of chronic pelvic pain syndromes

Chronic pelvic pain (new definition)	Pelvic pain syndrome (1)	Urological	Painful bladder syndrome (1)	Interstitial cystitis	
			Urethral pain syndrome (1)		
			Penile pain syndrome (new definition)		
			Prostate pain syndrome (Adopted from NIH) (3)		
			Scrotal pain syndrome (1)	Testicular pain syndrome (new definition)	
				Post-vasectomy pain syndrome (new definition)	
				Epididymal pain syndrome (new definition)	
		Gynaecological	Endometriosis-associated pain syndrome (new definition)		
			Vaginal pain syndrome (1)		
			Vulvar pain syndrome (1)	Generalized vulvar pain syndrome (ISSVD 1999)	
				Localized vulvar pain syndrome (ISSVD 1999)	Vestibular pain syndrome (ISSVD 1999)
					Clitoral pain syndrome (ISSVD 1999)
		Anorectal	Proctalgia fugax (2)		
			Anorectal pain syndrome (new definition)		
			Anismus		
		Neurological	Pudendal pain syndrome (new definition)		
		Muscular	Perineal pain syndrome (1)		
			Pelvic floor muscle pain syndrome (new definition)		
	Well-defined conditions that produce pain, examples include:	Urological	Infective cystitis		
			Infective prostatitis		
			Infective urethritis		
			Infective epididymo-orchitis		
		Gynaecological	Endometriosis		
		Anorectal	Proctitis		
			Haemorrhoids		
			Anal fissure		
		Neurological	Pudendal neuropathy		
			Sacral spinal cord pathology		
		Other	Vascular		
			Cutaneous		
			Psychiatric		

There is currently no ideal classification for those conditions that may be considered under chronic pain syndrome. The axes used above are based on the IASP classification (2). Much of the terminology comes from the ICS classification of chronic pain (1) with input from the ISSVD and the IASP special interest group, Pain of Urogenital Origin (PUGO) and Specialists in Pain International Network (SPIN). The major controversy within this area is that a pain may involve multiple sites, aetiologies and mechanisms.

An individual using the above classification should start on the left of the table and proceed to the right only if they can truly and confidently confirm the pathology in the appropriate system and organ. In many cases, it may not be possible to progress further than labelling a condition as pelvic pain syndrome. For instance, in many cases where patients have been given the label of 'prostadynia' in the past, it may not be possible to categorically state that the pain stems from the prostate and not other sites, such as the pelvic floor muscles. Those patients would thus have to be labelled with pelvic pain syndrome. Interstitial cystitis (IC) can be well defined (see within). However, many patients previously labelled as suffering from IC do not meet the research criteria and as a result would have to be labelled using Table 1 at some point to the left of IC, possibly

painful bladder syndrome.
The term ‘pain syndrome’ is used as primary pathology, may be well defined and at one site to start with. However, as the condition progresses, the picture may become more complicated and involve multiple sites and mechanisms. The condition then becomes a complex of symptoms and signs that is a syndrome.

The IASP axial classification is extended above and beyond the system used here to include temporal, intensity and aetiological characteristics. These descriptors should also be collected for audit and research purposes. At the request of the ISSVD, it should be noted whether or not the pain is provoked (see below Appendix).

This classification system aims to draw together the expertise of a number of specialist groups. This classification system will need to be revised significantly over the next few years.

Appendix - IASP classification as relevant to chronic pelvic pain

The IASP classification of chronic pelvic pain firstly identifies the region involved (Axis I), in this case the pelvis. Next, the main system involved (Axis II) is identified, which in the case of chronic pelvic pain is urological, gynaecological, anorectal, neurological or muscular. The ‘other’ system will allow expansion as more is understood about the condition. For a complete classification, the IASP system also includes a temporal, intensity and aetiological axis.

1. Axis III - temporal characteristics of pain and pattern of occurrence
    - not recorded, not applicable, or not known
    - single episode, limited duration
    - continuous or nearly continuous, non-fluctuating severity
    - continuous or nearly continuous, fluctuating severity
    - recurring irregularly
    - recurring regularly
    - paroxysmal
    - sustained with superimposed paroxysms
    - other combinations
    - none of the above

2. Axis IV - patient’s statement of intensity and time since onset of pain
    - mild
        - ≤ 1 month
        - 1-6 months
        - > 6 months
    - medium
        - ≤ 1 month
        - 1-6 months
        - > 6 months
    - severe
        - ≤ 1 month
        - 1-6 months
        - > 6 months

3. Axis V - aetiology where known, which may include a precipitating cause
    - genetic or congenital
    - trauma, operation, burns
    - infective, parasitic
    - inflammatory, immune
    - neoplasm
    - toxic, metabolic
    - degenerative, mechanical
    - dysfunctional (including psychophysiological)
    - unknown
    - psychiatric

4. Axis VI - provocation (suggested at the request of the ISSVD)
    - provoked
    - not-provoked

5.4 REFERENCES

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5.5 Chronic prostatitis

5.5.1 Introduction

Prostatitis is an obscure and poorly understood disease because limited physical access to the gland inhibits study. With no certainty about the aetiology, the absence of distinguishing clinical features, non-uniform diagnostic criteria and a protracted treatment course, a plausible explanation for the condition is far from our grasp. In approximately 5-10% of cases, clinical prostatitis is of proven bacterial aetiology. Where laboratory methods fail to identify causative bacteria in the other 90% of patients, the condition has been classified as 'chronic non-bacterial prostatitis' or 'prostatodynia' (1-3). An appreciation of the fact that the symptoms do not necessarily indicate isolated prostatic disease has led to a renaming: 'Chronic prostatitis associated with chronic pelvic pain syndrome' is the new term applied to patients with symptomatic prostatitis of non-bacterial origin (4). The reader is reminded that for the sake of clarity older terminology will be used freely in this report.

5.5.2 Definition

Chronic prostatitis associated with chronic pelvic pain syndrome is defined as discomfort or pain in the pelvic region with sterile cultures of specimens and insignificant white blood cell counts in prostate-specific specimens, namely semen, expressed prostatic secretions and urine collected after prostate massage (4). According to the new classification of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), chronic prostatitis associated with chronic pelvic pain syndrome is defined as category IIIB (5) (see table 2).

Table 2 Classification of prostatitis according to NIDDK/NIH

I.	Acute bacterial prostatitis (ABP)
II.	Chronic bacterial prostatitis (CBP)
III.	Chronic pelvic pain syndrome (CPPS)
	A. Inflammatory CPPS: WBC in semen/EPS/voided bladder urine-3 (VB3)
	B. Noninflammatory CPPS: no WBC semen/EPS/VB3
IV.	Asymptomatic inflammatory prostatitis (histological prostatitis)

5.5.3 Pathogenesis

The aetiology and pathophysiology of chronic prostatitis remains a mystery. Acute bacterial prostatitis is a different disease process to chronic prostatitis syndromes. As is frequently the case with pelvic pain syndromes, the story is dominated by hypotheses, all of which lack a substantial evidential standing.

Patients with chronic pelvic pain syndrome demonstrate no evidence of inflammation. They do not have urethritis, urogenital cancer, urethral stricture, or neurological disease involving the bladder. Indeed, they exhibit no overt renal tract disease (4).

Several hypotheses have been advanced to describe the aetiology of chronic prostatitis. Some have proposed that the pain and the subsequent irritative and obstructive voiding symptoms may be caused by lower urinary tract obstruction due to bladder neck problems, detrusor sphincter dysfunction, urethral stricture or dysfunctional voiding resulting in high pressure voiding (6-11). Others have described an intraprostatic ductal reflux caused by high pressure, turbulent voiding in combination with an anatomical abnormality (12-15).

A microbiological aetiology is held as a reasonable postulate. Some lower urinary tract commensals assumed to be harmless may yet be found to be pathogenic. More sensitive isolation methods may identify hitherto undetected infecting agents (4).

Some authors advocate immunological processes as the culprits in non-bacterial prostatitis, precipitated by an unrecognized antigen or an autoimmune process (16-18). Urinary reflux into the prostatic ducts and acini might stimulate a sterile inflammatory response (13).

A neuromuscular aetiology has also found favour (19-21). The symptoms may represent a type of reflex sympathetic dystrophy of the perineum and pelvic floor.

5.5.4 Diagnosis

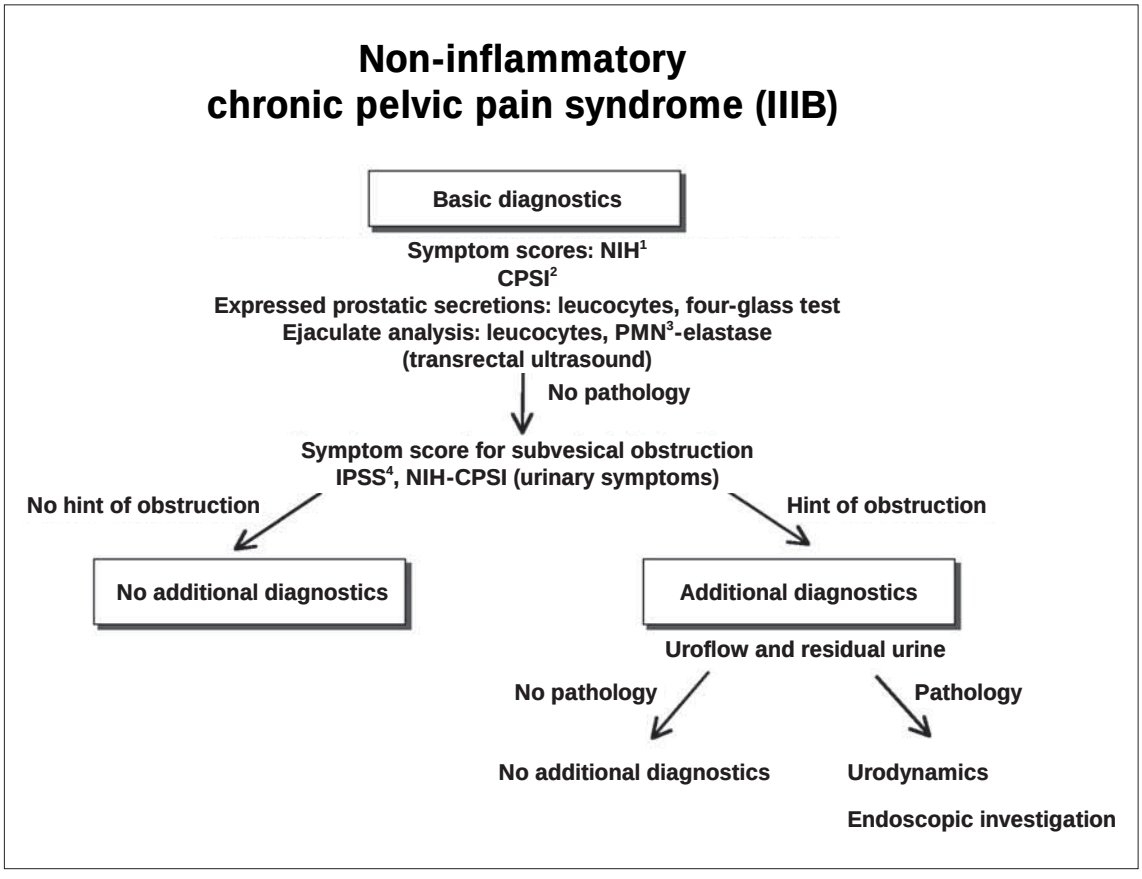
Despite the implications of the name, chronic prostatitis is a symptomatic diagnosis. It can be diagnosed based on a 3-month history of genitourinary pain and the absence of the other lower urinary tract pathologies described earlier. Determination of the severity of disease, its progression and the response to therapy can be assessed only by means of a validated symptom scoring instrument (22,23). In addition, a quality of life assessment is useful. It has been found that chronic prostatitis affects quality of life in a similar way to acute myocardial infarction, unstable angina pectoris or Crohn's disease (24,25). Reliable, valid indexes of symptoms and quality of life are the NIH Prostatitis Symptom Index (CPSI) (26) and the International Prostate Symptom Score (IPSS) (27).

In chronic prostatitis, urodynamic studies demonstrate decreased urinary flow rates, incomplete relaxation of the bladder neck and prostatic urethra, as well as abnormally high urethral closure pressure at rest. The relaxation of the external urethral sphincter during urination is normal (6,28).

Laboratory diagnosis is based on the four-glass test for bacterial localization ('gold standard') (29). However, this test is too complex to be used by the majority of practising urologists (4). Microscopic findings of the expressed prostatic secretions show numerous leucocytes and lipid-laden macrophages, but no organism is identified by microscopy or culture, and the bladder specimen is sterile (30). Diagnostic efficiency may be enhanced cost-effectively by a simple screening procedure (two-glass test) (31).

An overview of the diagnostic assessment of chronic prostatitis is shown in Figure 1.

Figure 1: Diagnostic assessment of chronic prostatitis



[1] NIH = National Institutes of Health
[2] CPSI = Chronic Prostatitis Symptom Index
[3] PMN = polymorphonuclear
[4] IPSS = International Prostate Symptom Score

5.5.5 Treatment

The cause of chronic prostatitis (syndrome category IIIB) is not known, so causal treatment is a problem and many therapeutic options are justified on the basis of anecdote alone. Cure is not currently a realistic goal so that symptom management is the only route to an improvement in quality of life (32).

A review of the literature suggest that alpha-blockers, muscle relaxants and various physical therapies improve symptoms (4,32).

Muscle relaxants (diazepam, baclofen) are reported to be helpful if sphincter dysfunction or pelvic floor/perineal muscle spasm is present, but there have been no prospective clinical trials to support these claims (33).

Small studies with alpha-blockers suggest that clinical improvement is seen in 48-80% of cases (6,21,34,35). Improving outflow performance by blocking the alpha-receptors of the bladder neck and prostate may relieve some of the symptoms.

Supportive therapy, such as biofeedback, relaxation exercises, lifestyle changes (i.e. diet, discontinuing bike riding), acupuncture, massage therapy, chiropractic therapy or meditation, have all be claimed to improve symptoms (4,32).

Because some patients have been observed to improve with antimicrobial therapy (3), a trial treatment with antibiotics is recommended (33,34). Patients responding to antibiotics should be maintained on the medication for 4-6 weeks or even longer. If relapse occurs after discontinuation, continuous low-dose antimicrobial therapy should be reintroduced and sustained if effective (37). Long-term results with trimethoprim-sulphamethoxazole have remained poor (38-40). Results of therapy with quinolone, including norfloxacin (41), ciprofloxacin (42,43) and ofloxacin (44-46), seem to be more encouraging.

Analgesics are used for most patients with prostatitis, but data on their long-term efficacy are limited (4,32).

Non-steroidal anti-inflammatory drugs may lead to favourable results in some patients. Immune modulation using cytokine inhibitors or other approaches may be helpful, but proper trials should be accomplished before this kind of therapy can be recommended (47,48).

Some small pilot studies with 5-alpha-reductase inhibitors support the view that finasteride may favourably influence voiding and pain (33,49,50).

Anticholinergics are beneficial in reducing irritative urinary symptoms and aiding normal sexual activity (51).

Positive effects of phytotherapy (52,53) and pentosanpolysulphate (PPS) (54) have been reported, but these options need to be explored in prospective studies before any recommendations can be made.

Heat therapy, such as transrectal hyperthermia (55-58) and transurethral thermotherapy (59-62), have been reported to induce favourable effects in some patients (32).

Surgical treatments such as transurethral incision of the bladder neck (9), radical transurethral resection of the prostate (63,64) or particularly radical prostatectomy have a very limited role and require an additional, specific indication (32).

5.6 Interstitial cystitis

5.6.1 Introduction

IC is a disease of the urinary bladder, which was first described by Skene in 1887 (65). The ulcer, which is a typical cystoscopic finding in 10-50% of IC patients, was first described by Guy L. Hunner at the beginning of the last century (66,67). It was also called a ‘submucous ulcer’, but the terminology of Skene (65) was readopted in 1930 by Bumpus, who considered this to be more appropriate due to the general involvement of the bladder (68). In 1949, when John Hand (69) presented a large series of IC patients with varying endoscopic and histopathological presentations, he realized that his material on IC did not comprise just one single entity.

5.6.2 Definition

An extremely wide variety of diagnostic criteria have been used because of the difficulties in defining the disease. In the late 1980s during a conference of the NIDDK, consensus criteria were established to ensure that the groups of patients enrolled in scientific studies would be relatively comparable (Table 3) (70). These criteria produce a diagnosis of IC by exclusion. Bladder pain, urgency and the finding of submucosal haemorrhages, called glomerulations, are the only positive elements. Identification of circumscribed lesions of the Hunner type is an automatic inclusion criterion. The NIDDK criteria are generally accepted, but represent a minimum framework to establish the diagnosis and have, by some, been felt to be too restrictive for clinical use (71). Others contend that precision can be increased by further identification of positive disease criteria. It has to be accepted that, whatever the method, heterogeneity seems currently unavoidable (72-74).

Table 3: Research definition of interstitial cystitis established by NIDDK Workshop on IC, 28-29 August 1987 (70)

Automatic inclusions

- Hunner's ulcer

Positive factors

- Pain on bladder filling relieved by emptying
- Pain (suprapubic, pelvic, urethral, vaginal or perineal)
- Glomerulations on endoscopy
- Decreased compliance on cystometrogram

Automatic exclusions

- < 18 years old
- Benign or malignant bladder tumours
- Radiation cystitis
- Tuberculous cystitis
- Bacterial cystitis
- Vaginitis
- Cyclophosphamide cystitis
- Symptomatic urethral diverticulum
- Uterine, cervical, vaginal or urethral cancer
- Active herpes
- Bladder or lower ureteral calculi
- Waking frequency < five times in 12 hours
- Nocturia < two times
- Symptoms relieved by antibiotics, urinary antiseptics, urinary analgesics (e.g. phenazopyridine hydrochloride)
- Duration < 12 months.
- Involuntary bladder contractions (urodynamics)
- Capacity > 400 mL, absence of sensory urgency

Bladder distension is defined arbitrarily as 80 cm water pressure for 1 minute (sic). Two positive factors are necessary for inclusion in the study population. Substratification at the conclusion of the study by bladder capacity with the patient under anaesthesia was < 350 mL and > 350 mL.

5.6.3 Pathogenesis

The aetiology of IC is unknown. Inevitably, hypotheses abound with evidence proving sparse.

Infection. No microorganism has been found to be the cause of IC. Although cultures of urine from a minority of IC patients may contain bacteria, antibiotic treatment is ineffective in this disease. Many studies have used sophisticated microbiological detection methods fruitlessly. It has been suggested that fastidious bacteria may be responsible (75), but several authors, such as Lynes and co-workers (76), have found no immunological evidence of recent or remote bacterial infection. Viral culture methods have been equally disappointing. Polymerase chain reaction (PCR) techniques probing for 16S rRNA genes that would be present if there were bacteria in bladder tissue or urine have drawn a blank (77). Nevertheless, the possibility of a microbiological contribution is not a closed book yet.

Inflammation seems to be an essential part of the picture in classic IC. Histological examination of bladder lesions has revealed pancystitis and perineural inflammatory infiltrates of lymphocytes and plasma cells (78). Inflammation is scant in non-ulcer IC (72).

Mast cell activation. Mast cells are multifunctional immune cells that contain highly potent inflammatory mediators, such as histamine, leukotrienes, serotonin and cytokines (79). Many of the symptoms and findings in classic IC, such as pain, frequency, oedema, fibrosis and neovascularization in the lamina propria, may be due to the release of mast cell-derived factors. There is a ten-fold increase in the mast cell count in bladder tissue from patients with classic IC compared with controls. In non-ulcer IC, however, the mast cell count is normal or only slightly increased (72,79,80).

Urothelial dysfunction/glycosaminoglycan (GAG)-layer defects. All patients with IC present with some kind of

fragility of the bladder mucosa, expressed as fissures or rupture of the bladder urothelium on distension (mucosal cracking). In classic IC, granulation tissue is also present indicating a reparative process (81). In patients with classic IC, urothelial detachment and gross defects of the urothelial lining are characteristic findings whereas, in some non-ulcer IC patients, multiple, superficial defects are seen after bladder distension (81). Widened tight junctions and increased permeability have been demonstrated by scanning electron microscopy and other techniques (82,83). These changes could be consistent with a defect in the GAG-layer. Such a hypothesis has been proposed by Parsons and Mulholland (84,85), who postulate that GAG-layer defects expose the submucosal nerve filaments to noxious chemicals from urine.

Autoimmune mechanisms. Numerous studies of autoantibodies have been performed in patients with IC (86), but the findings are far from specific. Some of the clinical and histopathological characteristics present in IC patients are similar to other autoimmune phenomena. Antinuclear antibodies have been described (87,88), which has led to hypotheses of a lupus-like reaction (89,90). In fact, only some IC patients demonstrate autoantibodies and the proposal that autoantibody titres could reflect disease severity in IC patients is untested (91).

Immune deposits in the bladder wall vasculature were found by Mattila (92). Other studies by the same group have implicated complement activation (93). By means of immunohistochemical and cytoflourometric analyses of the bladder mucosa, differences between classic and non-ulcer IC patients were demonstrated. In classic IC, intense T-cell infiltrates and B-cell nodules were seen, whereas only some T-cell infiltration was observed in non-ulcer IC (94). The poor description of patients in many studies, particularly when it comes to subtyping of IC patients, has not helped interpretation of these data.

Nitric oxide metabolism. Inevitably nitric oxide synthetase activity has been scrutinized (95). Oral administration of L-arginine (96) has been shown to increase nitric oxide-related enzymes and metabolites in the urine of patients with IC (97); however, the relevance of this is not apparent.

Neurobiology. An increase in the sympathetic innervation and activation of purinergic neurotransmission has been reported in IC patients. The S-100 family of proteins appears in Schwann cells of the peripheral nervous system (98). Decreased levels of S-100 protein were found in non-ulcer IC patients compared with controls (99). However, this finding conflicts with that of Hohenfellner et al. (100), who used “polyclonal antihuman protein gene product 9.5 antibody” and found that the overall nerve content increased in IC patients compared with controls. They did not subtype their patients as classic and non-ulcer forms.

Tyrosine hydroxylase is the rate-limiting enzyme for all catecholamine synthesis. An increase in tyrosine hydroxylase immunoreactivity in bladder tissue from IC patients but not controls has been described (101). This could be interpreted as a sign of increased sympathetic outflow.

A distinctive ultrastructural appearance of specimens from patients with non-ulcer IC prompted Elbadawi and Light to hypothesize neurogenic inflammation as a trigger to a cascade of events (102).

Toxic agents. Toxic constituents in the urine may cause injury to the bladder in IC. One hypothesis is that heat labile, cationic urine components of low molecular weight may exert a cytotoxic effect (103). Defective constitutive cytokine production may decrease mucosal defences to toxic agents (104).

Hypoxia. A decrease in the microvascular density in the suburothelium has been observed (105). In a recent study, it was found that bladder perfusion decreased with bladder filling in IC patients, but that the opposite occurred in controls (106).

Complex pathogenic interactions. In recent years, more complex, multifaceted mechanisms have been proposed. Theoharides et al. have shown that activation of mast cells in close proximity to nerve terminals can be influenced by oestradiol as well as corticotrophin releasing hormone (107). Okragly et al. found elevated levels of tryptase, nerve growth factor, neurotrophin-3 and glial cell line-derived neurotrophic factor in IC compared with controls (108). These findings prompted suggestions that IC may result from interactions between the nervous, immune and endocrine systems. Recently, it was proposed that the distribution of mast cells into the epithelium in classic IC could be explained by the epithelial co-expression of stem cell factor and interleukin-6 (IL-6) (79). According to Abdel-Mageed et al., an increased expression of p65, a nuclear factor-kappa B subunit, was found in patients with IC (109). They subsequently presented data showing a five-fold increase in the expression of the gene for IL-6 after activation of nuclear factor-kappa B (110), although IL-6 is a ubiquitous cytokine.

5.6.4 Epidemiology

Reports of the prevalence of IC have varied. The first systematic study indicated that IC affected approximately 10/100,000 population in Finland (111). Bade found a prevalence of 8-16/100,000 population in the Netherlands

(112). It has, however, been proposed that the prevalence of IC has been underestimated (113) and that it might exceed 0.5% among adults in the USA (69,111,114,116). Recent reports from the USA indicate that 5-6/10,000 population may be afflicted (117). Uncertainty arises through the use of purely symptomatic diagnostic criteria.

There is a female predominance of about 10:1 (69,111,115,116) and it seems that the disease is more common among Caucasians (116).

The relative proportions of classic and non-ulcer disease are unclear. Messing and Stamey reported that classic IC accounted for about half of all patients with IC (118). The same rate has been reported from Sweden (72,74). Centres in the USA with large patient databases have found that the Hunner type accounts for 5-10% of cases of IC (119). Koziol et al. recently presented a very large series from the USA in which classic IC accounted for approximately 20% of cases (120).

Evidence that IC may have a genetic component is increasing. According to Parsons (121), 35% of 466 patients with IC and 33% of 166 patients with urethral syndrome reported urgency/frequency problems in female relatives. Warren et al. (122) surveyed 2,058 patients of the Interstitial Cystitis Association (ICA) for first-degree relatives with IC and found a higher prevalence than in the general population. They also determined the concordance of IC among ICA twins (123); among the co-twins of eight monozygotic twin respondents, five had probable or confirmed IC, while none of 26 dizygotic co-twins were affected.

IC has significant economic costs. Excluding indirect costs, the incremental medical cost attributable to IC in the USA has been estimated to more than $100 million/year (113).

5.6.5 Association with other diseases

An association between IC and inflammatory bowel disease, systemic lupus erythematosus, irritable bowel syndrome and fibromyalgia has been reported (124-126).

5.6.6 Diagnosis

The diagnosis of IC is made on symptoms, examination, urine analysis, cystoscopy with hydrodistension and biopsy (Figure 2, see page 81).

All patients with IC present with characteristic pain and urinary frequency that is sometimes extreme and always includes nocturia. The character of the pain is the key symptom of the disease. Pain is related to the degree of bladder filling, typically increasing with increasing bladder content, located suprapubically, sometimes radiating to the groins, vagina, rectum or sacrum, and is relieved by voiding but soon returns (72,107,127-129).

The differences between the two subtypes include clinical presentation and age distribution (74). Classic IC is a destructive inflammation with some patients eventually developing a small capacity, fibrotic bladder or upper urinary tract outflow obstruction. There is no such progression in non-ulcer disease (118,130). The two subtypes express different histopathological, immunological and neurobiological features (80,81,94,99,101,131,132).

They may be discriminated non-invasively (120). The two subtypes respond differently to treatment (133-136).

Endoscopically, classic IC displays reddened mucosal areas often associated with small vessels radiating towards a central scar, sometimes covered by a small clot or fibrin deposit (72). The scar ruptures with increasing bladder distension with a characteristic waterfall type of bleeding. There is a strong association between classic IC and reduced bladder capacity under anaesthesia (72,74,137). Non-ulcer IC displays a normal bladder mucosa at initial cystoscopy. The development of glomerulations after hydrodistension is considered to be a positive diagnostic sign. A recent report showed that there is no difference in cystoscopic appearance between patients with non-ulcer IC and women without bladder symptoms about to undergo tubal ligation (138).

Biopsies are helpful in establishing or supporting the clinical diagnosis of both classic and non-ulcer types of IC. Important differential diagnoses to exclude by histological examination are carcinoma *in situ* and tuberculous cystitis (139).

A potassium chloride bladder permeability test has been reported to aid in the diagnosis of IC (140). However, according to recent reports, the test lacks discriminating power (141,142). The rhamnose absorption test has been suggested as a direct method of evaluating bladder permeability, but is still not corroborated in larger studies (143).

Symptom scores may be helpful tools to describe symptoms in an individual patient and to be used as outcome measures. The O'Leary-Sant symptom index has recently been validated successfully in a large study (144).

5.6.7 IC in children and males

According to the NIDDK criteria, age less than 18 years is an exclusion criterion. However, occasional cases of IC of both subtypes have been identified in younger patients (145). Thus, IC cannot be excluded on the basis of

age. Although there is a marked female predominance in IC, with a female to male ratio of 10:1, the diagnosis must also be considered in men presenting relevant symptoms (146).

5.6.8 Medical treatment

Analgesics. Since pain is a dominant symptom, commonly used analgesics are tried by most patients at some stage in the disease. Unfortunately, the results are generally discouraging, because visceral pain of the kind experienced in IC does not respond very well to such drugs. No systematic studies have been presented on conventional analgesics in IC. Long-term treatment with opioids for non-malignant processes is difficult but not infrequently used in patients with severe IC. Because of the chronic nature of the disease such drugs should be used only in exceptional cases and under close surveillance.

Corticosteroids have also been tried as a treatment for IC. Reports on outcome have been both promising (147) and discouraging (148). The side effects of steroids can be very serious so there is little justification for their use.

Anti-allergics. Mast cells are considered to play a role in IC. Among the substances released by mast cells is histamine. Histamine receptor antagonists have been used to block the H1-receptor subtype (149) as well as the H2-receptor (150), with variable results.

Hydroxyzine is a histamine H1-receptor antagonist that can block neuronal activation of mast cells by inhibition of serotonin secretion from thalamic mast cells and neurons (151). Usually, hydroxyzine hydrochloride (Atarax) is used, starting with 25 mg at bedtime, increasing the dose to 50 mg/day or even 75 mg, if tolerable. The most common side effects are sedation and generalized weakness, which normally resolve after a period of treatment. In the first series using this drug, more than 90% of patients responded with an improvement over the whole range of IC symptoms; interestingly, an improvement in associated symptoms such as migraine, irritable bowel syndrome and allergies was also noted (149). These promising results were corroborated in a further study (149,152).

Cimetidine, an H2-blocker, has been reported to improve symptoms in painful bladder syndrome (153). Thilagarajah et al. enrolled 36 patients with painful bladder diseases into a double-blind clinical study of oral cimetidine versus placebo for 3 months. Those receiving cimetidine had a significant improvement in symptom scores, pain and nocturia. However, histologically, the bladder mucosa showed no qualitative changes in either group (154).

Amitriptyline. The tricyclic antidepressant amitriptyline has been reported to alleviate symptoms in IC. The drug is thought to act via mechanisms such as blockade of the acetylcholine receptors, inhibition of released serotonin and norepinephrine reuptake, and blockade of the histamine H1-receptor. It is also an anxiolytic (155). Several reports have indicated amelioration of IC after oral treatment with amitriptyline (133,156,157).

Sodium pentosanpolysulphate (PPS; Elmiron) has been evaluated in double-blind, placebo-controlled studies. Subjective improvement of pain, urgency and frequency, but not nocturia, was reported in patients taking the drug compared with placebo (158,159).

In an open multicentre study, Fritjofsson et al. demonstrated that PPS had a more favourable effect in classic than in non-ulcer IC (136). PPS is thought to substitute for a defect in the glycosaminoglycan (GAG) layer. The normal dose is 150-200 mg twice daily between meals. Absorption is incomplete.

Antibiotics have a limited role in the treatment of IC. Warren conducted a prospective, randomized, double-blind, placebo-controlled pilot study of sequential oral antibiotics in 50 IC patients. Overall improvement was reported by 12 of 25 patients in the antibiotic group and 6 of 25 in the placebo group, while 10 and 5 patients, respectively, noticed an improvement in pain and urgency. The authors concluded that antibiotics alone or in combination may be associated with decreased symptoms in some patients, but do not represent a major advance in therapy for IC (160).

Prostaglandin. Misoprostol is a prostaglandin that regulates various immunological cascades. Kelly treated 25 IC patients with 600 μg of misoprostol daily for 3 months. Upon response, patients continued therapy for another 6 months. At 3 months, 14 had significantly improved, and after a further 6 months, 12 of them had a sustained response. However, the incidence of adverse drug effects was 64% (161).

L-arginine. Oral treatment with L-arginine, the substrate for nitric oxide synthase, has been reported to result in a decrease in IC-related symptoms (162-165). Nitric oxide has been shown to be elevated in patients with IC

(165). However, other investigators could not demonstrate either symptomatic relief or a change in nitric oxide production after treatment (166,167).

Immunosuppressants. Azathioprine has been tried as a treatment for IC by Oravisto and Alftan (168). They gave 38 patients 50-100 mg of azathioprine daily. Pain disappeared in 22 patients and urinary frequency in 20 patients. However, because side effects were not reported and controlled trials are unavailable, the published data are insufficient to assess the value of this treatment in IC. More recently, cyclosporin (169) and methotrexate (170) have been evaluated in open studies and have had a good effect on pain, but limited effect on urgency-frequency.

Anticholinergics. Oxybutynin is an anticholinergic drug used to treat overactive detrusor dysfunction. In one study, intravesical administration of oxybutynin combined with bladder training resulted in an improvement in functional bladder capacity, volume at first sensation and cystometric bladder capacity (171). However, the effect on pain was not reported.

Gabapentin. The antiepileptic drug gabapentin is a new agent that is also used in the adjunctive treatment of painful disorders. Gabapentin may reduce the need for co-therapeutics, such as opioids. Two patients with IC showed improved functional capacity and received adequate pain control with the addition of gabapentin to their medication regimen (172). In a subsequent uncontrolled, dose-escalation protocol involving 21 patients with chronic genitourinary pain (173), 10 patients had improved with gabapentin at 6 months. The study included eight IC patients of whom five responded to gabapentin.

Suplatast Tosilate is an oral immunoregulator that suppresses helper T-cell mediated allergic processes. Ueda et al. (174) examined the efficacy of Suplatast Tosilate (IPD-1151T) in 14 women with IC who reported a significantly increased bladder capacity and decreased symptoms after 1 year of treatment. No major side effects occurred and therapeutic effects correlated with a reduction in blood eosinophils, immunoglobulin E, and urinary T-cells. Comparative controlled data are unavailable.

Quercetin is a bioflavinoid that has been suggested to be effective in male pelvic pain syndrome. It was tested in a limited, open label study with hopeful results (175).

5.6.9 Intravesical treatment

Intravesical application of medications establishes high concentrations at the target site with few systemic side effects. The need for intermittent catherization, which can be painful in IC patients, the costs and the risk of infection are drawbacks. Various intravesical treatments have been proposed and investigated for IC.

Local anaesthetics. Sporadic reports of successful treatment of IC with intravesical lidocaine can be found in the literature (176,177). Lidocaine has an anaesthetic effect on the urothelium, but is poorly absorbed. According to Henry (178), superior pharmacokinetics can be achieved by alkalization of lidocaine prior to intravesical application.

PPS is a glycoprotein aimed at replenishing the GAG layer in bladders affected by IC. The bioavailability of PPS is poor after oral administration, hence the intravesical application. A double-blind, placebo-controlled study (179) was performed in 20 IC patients, of whom 10 received intravesical PPS (300 mg in 50 mL of 0.9% saline) twice a week for 3 months and 10 received placebo. At 3 months, four patients in the PPS group and two patients in the placebo group gained significant symptomatic relief. Bladder capacities showed a statistically significant increase only in patients treated with PPS. At 18 months, symptoms were relieved in eight patients who were still receiving PPS instillations and in four patients who were not receiving treatment.

Intravesical heparin was proposed as a coating agent. In an open, prospective, uncontrolled trial (180), 48 IC patients received instillations of 10,000 units in 10 mL of sterile water, three times a week for 3 months. In over half of the patients studied, intravesical heparin controlled the symptoms of IC with continued improvement even after 1 year of therapy. Kuo (181) reported another uncontrolled trial of intravesical heparin (25,000 units twice a week for 3 months) in women with frequency-urgency syndrome with a positive potassium test. The study included 10 patients with IC of whom eight reported symptomatic improvement.

Hyaluronic acid. Treatment with hyaluronic acid, a natural proteoglycan, is aimed at repairing defects in the GAG layer. Morales (182) treated 25 IC patients and reported a response rate of 56% at week 4 and 71% at week 7. After week 24, effectiveness decreased, but there was no significant toxicity. Nordling (183) reported a 3-year follow-up to a 3-month, prospective, non-randomized study evaluating the effect of intravesical

hyaluronic acid on IC symptoms. Of the 20 IC patients, 11 chose to continue treatment beyond the initial trial, and modest beneficial long-term effects were noted in about two-thirds of patients.

Dimethyl sulphoxide (DMSO) is a chemical solvent and water soluble liquid that penetrates cell membranes and is claimed to have analgesic, anti-inflammatory, collagenolytic and muscle relaxant effects. It is also a scavenger of the intracellular OH radical that is believed to be an important trigger of the inflammatory process. It has been tested empirically and found to alleviate symptoms in IC, and is now a standard treatment. In a controlled, crossover trial (184), 33 IC patients received instillations of a 50% DMSO solution and placebo (saline). All patients received both regimens, which were administered intravesically every 2 weeks for two sessions of four treatments each. Subjective improvement was noted in 53% of patients receiving DMSO versus 18% receiving placebo, and objective improvement in 93% and 35%, respectively. Other uncontrolled trials with DMSO have reported response rates of 50-70% for a period of between 1 and 2 months (185). DMSO is contraindicated during urinary tract infections or shortly after bladder biopsy, and it temporarily causes a garlic-like odour. It should also be noted that a case in which DMSO treatment may have caused pigmented eye lens deposits has been reported (186), so that ophthalmic review should be considered during treatment.

Bacillus Calmette-Guérin (BCG). The immunomodulatory properties of the tuberculosis vaccine bacillus Calmette-Guérin (BCG) are used in the intravesical treatment of superficial bladder carcinoma. In 1997, a prospective, double-blind pilot study of intravesical BCG demonstrated a 60% response rate with BCG compared with placebo in 30 IC patients who received 6-weekly instillations of Tice strain BCG or placebo (187). In a subsequent 24-33-month follow-up report, eight of the nine responders reported favourably and BCG did not worsen symptoms in non-responders (188). These results are at variance with those of a prospective, double-blind crossover trial of BCG and DMSO (135), in which BCG treatment failed to demonstrate any benefit.

Clorpactin is a detergent of hypochloric acid that was employed in the treatment of tuberculous cystitis (189) and was used for the treatment of IC 50 years ago (190,191). Its mode of action is based on urothelial destruction followed by a reconstitution of supposedly healthy tissue. Instillations of a 0.4% solution of clorpactin have reportedly provided effective and long-lasting relief of IC symptoms (192,193). The procedure is painful and requires anaesthesia. Treatment initially worsens symptoms of pain and dysuria for several days. Weekly-to-monthly treatment intervals have been suggested and response rates range from 50-70% for a period of between 6 and 12 months (194). The treatment is contraindicated after recent bladder biopsy and in patients with vesicoureteral reflux, since ureteral fibrosis may result (192,195). There is a high complication rate.

Vanilloids disrupt sensory neurons (196). Resiniferatoxin (RTX) is an ultrapotent analogue of the chilli pepper extract capsaicin, which causes less pain on instillation. In a randomized, placebo-controlled trial in 18 patients with hypersensitive bladder disorder and pain (197), RTX significantly reduced mean frequency, nocturia and pain scores by approximately 50%. In another study of seven patients with detrusor hyperreflexia, RTX improved urinary frequency, incontinence and bladder capacity (198).

5.6.10 Interventional treatments

Bladder distension. A frequently cited report by Bumpus (68) claims imprecisely that hydrodistension achieved symptom improvement in 100 patients over several months. Neither patient population nor symptoms were defined, and the description of the methods used is inadequate. Ormond (199) and Longacre (200) were equally inexact during the 1930s. In 1957, an uncontrolled retrospective study was presented by Franksson (201), who treated 33 patients with repeated, up to 10-fold distensions. Symptoms improved in 12 patients for up to 4 weeks, in 14 patients for up to 6 months and in seven patients for up to 1 year. British studies from the 1970s reported contradictory results. Dunn (202) claimed to have achieved complete absence of symptoms in 16 of 25 patients during a mean follow-up of 14 months using the Helmstein method (203), where an intravesical balloon is distended at the level of systolic blood pressure for 3 hours. Bladder rupture occurred in two cases. These results disagree with those of Badenoch (147), who failed to note any improvement in 44 of 56 patients after hydrodistension. Twenty years later, McCahy (204) rejected balloon hydrodistension because of inefficacy and a complication rate of 20%.

In a recent study, Glemain (205) reported an uncontrolled study of 65 IC patients treated with 3-hour balloon hydrodistention. Treatment efficacy in the 33 retrospectively- and 32 prospectively-studied patients was 38% and 60% at 6 months, and 22% and 43% at 1 year, respectively. The results were superior for bladder capacities above 150 mL.

Although hydrodistension of the bladder is a common treatment for IC, scientific justification is

lacking. It represents a diagnostic tool, but has a limited therapeutic role.

Electromotive drug administration (EMDA) enhances tissue penetration of ionized drugs by iontophoresis. Adapted for the bladder, it uses a transurethral anode and a suprapubic skin cathode.

Gurpinar (206) treated six IC patients with EMDA using lidocaine (1.5%) and 1:100,000 epinephrine in aqueous solution, while dilating the bladder to maximum tolerance. Significant bladder enlargement was achieved, and voiding symptoms and pain decreased. In four patients, the results were reported as 'durable'. Rosamilia (207) treated 21 women with IC with EMDA using lidocaine and dexamethasone, followed by cystodistension. A good response was seen in 85% of patients at 2 weeks, with 63% still responding at 2 months. Complete resolution of pain was achieved in 25% of patients reviewed at 6 months. Using a similar technique, Riedl (208) noted complete resolution of bladder symptoms in eight of 13 IC patients, which lasted 1-17 months. Partial or short-term improvement was observed in three patients. Two patients experienced aggravation of pain for several days after therapy. A 66% increase in bladder capacity was observed. When symptoms recurred, the treatment was repeated with equal efficacy in 11 patients.

EMDA is expensive and the subject of uncontrolled studies only.

Transurethral resection (TUR) coagulation and transurethral laser. Endourological ablation of bladder tissue aims to eliminate urothelial lesions, mostly Hunner ulcers. In a case report, Kerr (209) described a transurethral resection of a 1-cm ulcer in a woman who experienced symptom resolution for 1 year. Subsequently, Greenberg et al. (115) reported on 77 patients with Hunner ulcers treated over a 40-year period: 42 were managed conservatively, seven underwent fulguration and 28 were treated by TUR in a non-randomized fashion. Fulguration improved symptoms in five of seven patients. All patients experienced symptom recurrence in less than 1 year and efficacy was not superior to non-surgical treatment.

In another series of 30 classic IC patients (210), complete TUR of visible lesions resulted in initial disappearance of pain in all patients and a decrease in frequency in 21 patients. A relapse was noted in one-third of patients after 2-20 months, while the remaining two-thirds were still pain-free after 2-42 months. The same group recently reported the largest series of patients with classic IC treated with complete TUR of all visible ulcers (211). Altogether 259 TURs were performed on 103 patients; 92 experienced amelioration and symptom relief lasted more than 3 years in 40%. The majority of the remaining patients responded well to subsequent TUR.

Transurethral application of the neodymium-YAG laser is suggested as an alternative to TUR for endoscopic treatment in IC. Shanberg et al. (212) initially treated five refractory IC patients, of whom four demonstrated cessation of pain and frequency within several days. Follow-up at 3-15 months revealed no relapse except mild recurrent voiding symptoms. This series was extended to 76 patients treated at two institutions (213). Although 21 of 27 patients with Hunner ulcers noted symptom improvement, 12 experienced relapse within 18 months. In the group without ulcers, only 20 of 49 patients improved, of whom 10 required further therapy within 1 year.

Recently, Rofeim et al. (214) investigated 24 patients with refractory classic IC undergoing ablative Nd-YAG laser ablation of Hunner's ulcers. All patients had symptom improvement within days without complications. At 23 months, mean pain and urgency scores, nocturia, and voiding intervals had improved significantly. However, relapse in 11 patients required up to four additional treatments.

Endourological resections are not applicable to non-ulcer IC. These techniques may provide long-term alleviation of symptoms, but none are a cure for the disease. Controlled studies are still lacking.

5.6.11 Alternative and complementary treatments

Bladder training. For IC patients with predominant symptoms of frequency/urgency, but hardly any pain, behavioural bladder training techniques are attractive. Parsons et al. (215) included 21 selected IC patients on a protocol which focused on progressively increasing micturition intervals. Fifteen patients reported a 50% decrease in urgency, frequency and nocturia, and there was a moderate increase in bladder capacity. Chaiken et al. (216) retrospectively analysed 42 IC patients who were instructed in diary keeping, timed voiding, controlled fluid intake and pelvic floor muscle training. After 12 weeks, voiding intervals increased by a mean of 93 minutes and daily micturitions were reduced on average by nine voids. Overall, 88% of patients reported markedly improved or improved symptoms.

Dietary restrictions are among the many physical self-care strategies that IC patients are reported to develop (217). In an analysis of the Interstitial Cystitis Data Base (ICDB) cohort study, special diets rank in the five most commonly used therapies for IC (218). Bade et al. (219) investigated the nutritional habits of IC patients and found that they consume significantly fewer calories, and less fat and coffee, but more fibre. Comprehensive instructions on how to identify individual trigger foods are given in the IC-Network Patient Handbook (220).

Scientific data on a rationale for such diets are unavailable.

According to Gillespie (221), the concentration of certain metabolites and amino acids appears to be changed in patients with IC. A study of the metabolism of the arylalkylamines (tryptophan, tyrosine, tyramine, phenylalanine) in 250 IC patients revealed an inability to synthesize normal amounts of serotonin and a noradrenaline metabolite. In this study, dietary restriction of acid foods and arylalkylamines lessened the symptoms, but did not alter specific abnormalities in dopamine metabolism.

In another non-randomized, prospective study of IC patients with nutrition-related exacerbations, calcium glycerophosphate was reported to ease food-related flares (222). However, the observed efficacy seems little better than would be expected with placebo.

Overall, dietary management is a common self-care strategy in IC and offers a cost-effective therapeutic approach. Scientific data are, however, limited and dietary restriction alone will not result in complete relief of symptoms.

Acupuncture. In non-curable and agonizing diseases, such as IC, desperate patients frequently seek access to complementary medicine, such as acupuncture. However, scientific evidence for such treatments is often poor.

Chang performed urodynamics before and after acupuncture in 52 women with frequency, urgency and dysuria and reported a significant increase in capacity. Depending on the acupuncture site, symptomatic improvement was noted in up to 85% of patients (223). In a follow-up investigation after 1 and 3 years (224), these effects were no longer detectable and the authors concluded that repeated acupuncture was necessary to maintain the beneficial effects.

In a non-randomized comparison of females with urethral syndrome, 128 patients treated by acupuncture and traditional Chinese medicine were compared with 52 patients treated by Western medicine as controls. Efficacy rates and urodynamic parameters were significantly better in the acupuncture group (225). In contrast, in a prospective study of the effect of acupuncture in IC (226), no differences in frequency, voided volumes, or symptom scores were noted, and only one patient improved for a short period of time.

In summary, the few low-evidence reports on acupuncture in the treatment of IC are contradictory, and the effects appear to be limited and temporary.

Hypnosis is a therapeutic adjunct in the management of cancer, surgical disease and chronic pain. While it may be used in urological patients (227,228), no scientific data on the effect of hypnosis on IC symptoms have been reported.

5.6.12 Surgical treatment

When all efforts fail to relieve disabling IC symptoms, surgical removal of the diseased bladder represents an option (229-232). Three major techniques of bladder resection are common: supratrigonal (i.e. trigone-sparing) cystectomy, subtrigonal cystectomy, or radical cystectomy including excision of the urethra. All techniques require substitution of the excised bladder tissue, which is mostly performed with bowel segments.

Techniques without bladder removal. As early as 1967, Turner-Warwick reported that mere bladder augmentation without removal of the diseased tissue would not seem appropriate (233). Sporadic reports that unresected IC bladders will cease to cause symptoms when excluded from the flow of urine are scarce (118,234).

Supratrigonal cystectomy with subsequent bladder augmentation represents the most favoured continence-preserving technique for the surgical management of IC. Various intestinal segments have been used for trigonal augmentation including ileum (147,235-242), ileocaecum (241-248), right colon (147,242,249) and sigmoid colon (236,239,244,248). Substituting gastric segments (250,251) appears to be less advantageous, since the production of acids may maintain dysuria and persistent pain.

The therapeutic success of supratrigonal cystectomy has been reported in numerous studies. In 1966, Garrelts reported excellent results in eight of 13 patients with a follow-up of 12-72 months (238). In 1977, Bruce achieved satisfactory relief of IC symptoms by ileocystoplasty and colocystoplasty in eight patients (236). Dounis reported seven IC patients whose pain and frequency were considerably improved after supratrigonal cystectomy with ileocecal augmentation (252).

In 1991, Kontturi used segments of colon and sigmoid colon in 12 cases (248). All five patients augmented with sigmoid colon remained symptom free over 4.7 years of follow-up. Two of seven cases augmented with colon required secondary cystectomy with formation of an ileal conduit. Nielsen reported a series of eight patients undergoing supratrigonal cystectomy with ileocaecocystoplasty. While symptoms resolved in two patients, treatment failure in another six patients necessitated secondary cystectomy and ileal conduit formation (243).

Linn (253) followed six IC patients after supratrigonal cystectomy with an ileocecal augmentation for a

period of 30 months, and reported that all were symptom-free and voided spontaneously.

In 2002, Van Ophoven (229) reported the long-term results of trigone-preserving cystectomy and consecutive orthotopic substitution enteroplasty in 18 women with IC, using ileocecal (n = 10) or ileal (n = 8) segments. At a mean follow-up of nearly 5 years, 14 patients were completely pain-free, 12 voided spontaneously and 15 reported complete resolution of dysuria. Ileocecal bowel segments showed superior functional results since, in the group augmented with ileum, three patients required self-catheterization and one a suprapubic catheter. Overall, surgery achieved a significant improvement of diurnal and nocturnal frequencies, functional bladder capacity and symptom scores with only two treatment failures.

Subtrigonal cystectomy. Although less popular, the use of subtrigonal cystectomy in the management of IC has been reported (253-257). Subtrigonal resection has the potential of removing the trigone as a possible disease site, but at the cost of requiring ureteral reimplantation with its associated risks of leakage, stricture and reflux.

Nurse et al. reported trigonal disease in 50% within their cohort (13 of 25) and blamed surgical failures on the trigone left in place (258). In contrast, Linn et al. indicated that the level of resection is not solely responsible for treatment success. While completely curing six patients by supratrigonal resection, he noted three failures among 17 subtrigonal resections. Furthermore, half of the successful subtrigonal resections required self-catherization to support voiding of the ileocecal augmentate (253).

Selecting patients and technique. IC is benign and not lifetime-limiting, and thus operative procedures rank last in the therapeutic algorithm. However, severely refractory patients who are suffering should not have to tolerate unsuccessful conservative treatments for years when surgical options are available. Detailed consulting and informed consent must precede any irreversible type of major surgery, which should only be undertaken by experienced surgeons. The choice of technique will be influenced by the experience of the surgeon. The appropriate extent of tissue resection should be based on the endoscopic and histopathological findings. Some surgeons recommend preoperative cystoscopy and bladder capacity as a prognostic parameter for operative success (234). Nielsen (243), for example, noted that responders and failures following orthotopic substitution differed in mean preoperative bladder capacity (200 mL versus 525 mL, respectively). This observation is in agreement with the report by Peeker et al. (259), who found that patients with end-stage classic IC had excellent results following ileocystoplasty, while patients with non-ulcer disease were not helped by the procedure.

Cystectomy with formation of an ileal conduit stills ranks first in current US practice trends in surgical IC therapy (260). For cosmetic reasons, however, techniques of continent diversion seem preferable, particularly in younger patients. After orthotopic bladder augmentation, particularly when removing the trigone, voiding may be incomplete and require intermittent self-catherization. Therefore patients considering such procedures should be advised accordingly and must be considered capable of performing, accepting and tolerating self-catherization.

A summary of the treatment options for IC, including a rating of the level of evidence and grade of recommendation (Table 4) is given in Tables 5 and 6.

Table 4: Level of evidence and grade of recommendation

Level	Type of evidence
1a	Meta-analysis of randomized trials
1b	At least on randomized trial
2a	One well-designed controlled study without randomization
2b	One other type of well-designed quasi-experimental study
3	Non-experimental study (comparative study, correlation study, case reports)
4	Expert committee, expert opinion

Grade	Basis for recommendation
A	Clinical studies of good quality and consistency including at least one randomized trial
B	Well-conducted clinical studies without randomized trials
C	Absence of directly applicable clinical studies of good quality

Table 5: Medical treatment of IC

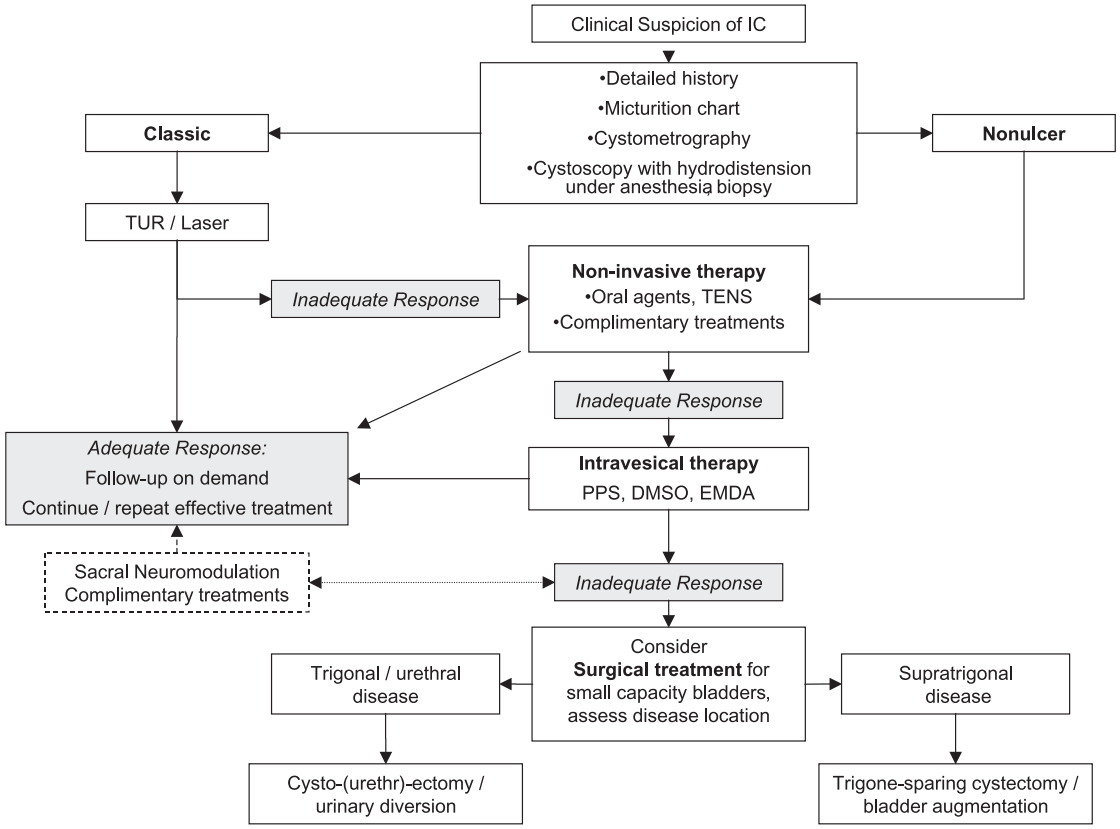
	Level of evidence	Grade of recommendation	Comment
Analgesics	2	C	Indications limited to cases awaiting further treatment
Corticosteroids	3	C	Corticosteroids not recommended as long-term treatment
Hydroxyzine	2b	B	Standard treatment
Cimetidine	1b	A	Preliminary data so far
Amitriptyline	1b	B	Standard treatment
Sodium PPS	1a	A	Standard treatment
Antibiotics	1b	A	Limited role in the treatment of IC
Prostaglandins	3	C	Insufficient data on IC, adverse effects
L-arginine	1b	C	Effect in IC uncertain
Immunosuppressants	3	C	Insufficient data on IC, adverse effects
Oxybutynin	3	C	Limited indication in IC
Tolterodine	3	C	Limited indication in IC
Gabapentin	3	C	Preliminary data so far
Suplatast Tosilate	3	C	Preliminary data so far
Quercetin	3	C	Preliminary data so far

Table 6: Intravesical, interventional, alternative and surgical treatment of IC

	Level of evidence	Grade of recommendation	Comment
Intravesical anaesthetics	3	C	
Intravesical PPS	1b	A	
Intravesical heparin	3	C	
Intravesical hyaluronic acid	3	B	
Intravesical chondroitin sulfate	3	B	
Intravesical DMSO	1b	A	
Intravesical BCG	1b	Not recommended beyond clinical trials	Data contradictory
Intravesical Clorpactin	3	Not recommended	Obsolete
Intravesical vanilloids	1b	Not recommended beyond clinical trials	Insufficient data on IC
Bladder distension	3	C	
EMDA	3	B	
TUR coagulation and laser	n.a.	A/B	Hunner's ulcers only
Nerve blockades/epidural pain pumps	3	C	For crisis intervention, effect on pain only
Sacral neuromodulation	3	B	Not recommended beyond clinical trials
Bladder training	3	B	Patients without pain
Manual and physical therapy	3	B	
Diet	3	C	
Acupuncture	3	C	Data contradictory
Hypnosis		No data	
Psychological therapy	3	B	
Surgical treatment	n.a.	A	Ultima ratio, experienced surgeons

n.a. = not applicable

Figure 2: Flowchart of the diagnosis and therapy of IC



5.7 Scrotal pain

5.7.1 Introduction

Acute scrotal pain includes torsion of the testis or appendices and requires immediate diagnostic and therapeutic attention. Chronic scrotal pain is a common source of complaint in urology clinics. Although it is not life threatening, its manifestations affect the patient's quality of life. As no epidemiological studies have been conducted, the prevalence of this symptom is unknown.

The pain has to have lasted for a minimum of 6 months to qualify as chronic scrotal pain. It can be unilateral or bilateral, and continuous or intermittent. It is not uncommon for examination to localize the site and to distinguish between testicular and epididymal pain.

5.7.2 Innervation of the scrotum and the scrotal contents

Because nerve blocks may modify the pain, a description of testicular innervation is relevant (see Section 10.3). Afferent innervation is via the genitofemoral nerve, which has a femoral branch to the skin of the ventromedial region of the thigh and a genital branch to the scrotal region. The ilioinguinal nerve conveys sensation from the groin region (261). The ilioinguinal and genitofemoral nerves are, however, subject to a great deal of anatomical variability (262). The pudendal nerve supplies the skin of the perineum.

According to the traditional view, the testes receive sympathetic input from the para-aortic ganglia. Studies using biochemical methods indicate that efferent fibres reaching the testes derive from the major pelvic and accessory pelvic ganglia (263). The nociceptive threshold may vary in response to physiological and psychosocial influences.

5.7.3 Clinical examination

A gentle palpation should be performed to identify each component of the scrotum. If possible, the site of pain should be localized. A digital rectal examination is mandatory and the integrity of the pelvis and spine should be examined. As a rule, ultrasonography (scrotum, prostate, urinary tract) should be performed, particularly to look for lesions within the testicular parenchyma and epididymal changes (264). The urine should be analysed. MRI and CT scans are options to augment assessment (265).

5.7.4 Differential diagnoses

Palpable intra-scrotal lesions:

- testicular tumour (rarely painful except, for example, when complicated by bleeding)
- hydrocele (rarely painful except, for example, when causing increased capsule tension)
- spermatocele (rarely painful except, for example, when causing increased capsule tension)
- cysts within the epididymis, tunica albuginea or spermatic cord
- varicocele (266).

Lesions evident on ultrasound:

- hypo-/hyperechoic areas, non-homogeneity
- microlithiasis of the testis (its relevance is still unknown) (267,268).

Previous surgery:

- hernia repair (269)
- vasectomy (post-vasectomy pain syndrome) (270).

Extragenital lesions:

- vertebral disease (271,272)
- lower ureteric stones
- aortic or iliac aneurysm (273)
- constipation in children (274).

Hypermobility of the testis:

- subtorsion.

Neurogenic causes:

- entrapment of the pudendal nerve (pain in seated position, cyclists) (275).

Chronic pelvic pain of unknown cause:

- subdivided into scrotal pain, testicular pain, epididymal pain syndromes.

5.7.5 Treatment

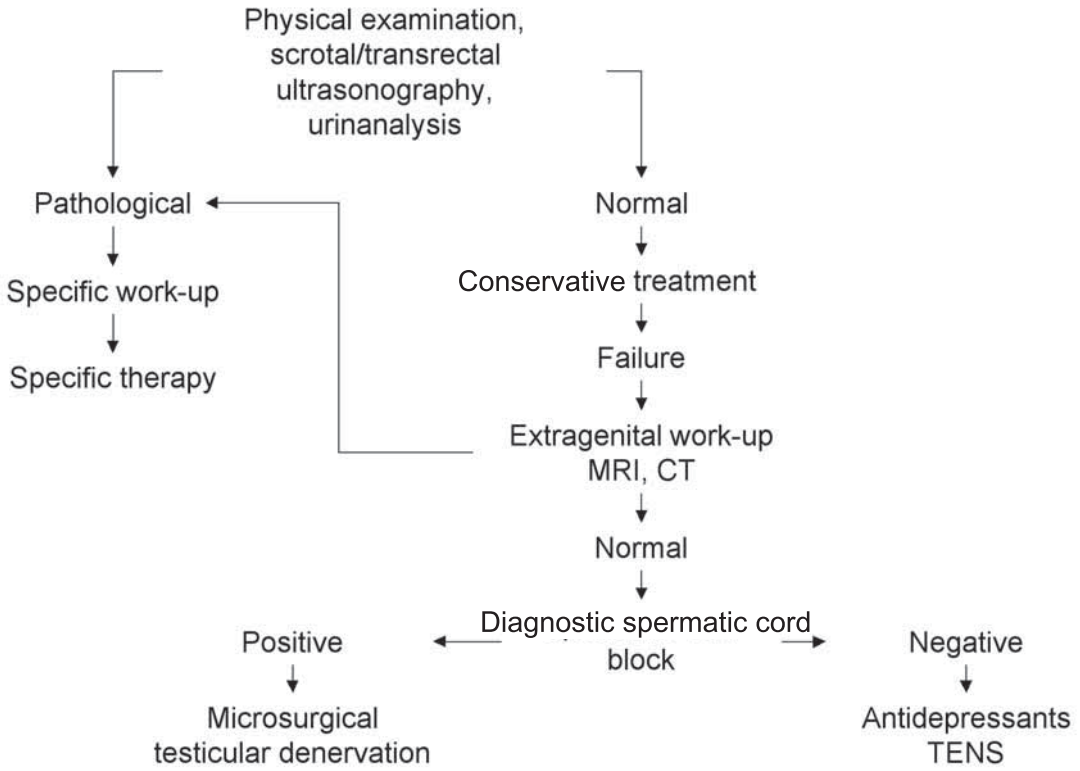
Patients with extragenital disease are treated according to the cause.

Patients with an identifiable intrascrotal lesion can be cured by a surgical procedure with a success rate of 50% on average (278). Superior results are obtained in the treatment of conditions such as painful hydrocele, spermatocele and varicocele (276,277).

Patients without identifiable lesions must primarily be treated conservatively (adjuvant antibiotics, analgesics (see Section 10.1), transcutaneous electrical nerve stimulation, nerve blocks). If these are unsuccessful, surgery can be considered. However, the results of epididymectomy and orchiectomy are poor (20% and 60% success rates, respectively) (278,279). Microsurgical testicular denervation represents another therapeutic option and favourable results have been reported (280,281). It has been suggested that patients with microcalcifications should be kept under surveillance because of a possible increased risk of testicular malignancy (268).

An overview of the diagnostic and therapeutic assessment of chronic scrotal pain is shown in Figure 3.

Figure 3: Flowchart for the diagnosis and therapy of chronic scrotal pain



5.8 Urethral syndrome

Urethral syndrome represents a less well-defined entity. Positive diagnostic signs are urethral tenderness or pain on palpation and a slightly inflamed urethral mucosa found during endoscopy. Hypotheses of the aetiology include concealed infections of the periurethral glands or ducts according to the anatomical description by Huffman (282), and oestrogen deficiency. Others refer to urethral syndrome as a manifestation of a less severe form of 'early' IC (121).

In clinical practice, the diagnosis of urethral syndrome is commonly given to patients who present with the symptoms of dysuria (with or without frequency, nocturia, urgency and urge incontinence) in the absence of evidence of urinary infection. It is the latter phrase that results in difficulties because the methods typically used to identify urinary infection are extremely insensitive.

Dysuria is pain or discomfort experienced in association with micturition. The classical symptom of a burning sensation in the urethra during voiding caused by infection is well known. Less appreciated is the external dysuria experienced by women with vaginitis when urine passes over the labia.

The biochemical testing and microbiological culture of urine is important in the assessment of lower urinary tract symptoms. This has recently been reviewed in some detail in relation to the elderly (283).

Confusion exists over the concept of significant bacteriuria, which may be accepted as 10^5 colony-forming units (CFU) of a single species in asymptomatic women, but may be as low as 10^2 CFU of a single

species of a known urinary pathogen in symptomatic women. Many automated culture systems have a sensitivity of 10^4 CFU, and urinary leucocyte esterase and nitrite tests correlate only with cultures as high as 10^5 CFU (284). In addition, many laboratory culture systems will detect only just over 50% of infections in midstream urine specimens from genuinely infected patients (284).

A narrow spectrum of aetiological agents causes 85-90% of cases of acute, uncomplicated cystitis in women. Nearly one-third of acutely dysuric women with urinary tract infections caused by *Escherichia coli, Staphylococcus saprophyticus*, or *Proteus spp*. have midstream colony counts in the range of 10^2-10^4 bacteria/mL. Investigators have also identified causative organisms by more invasive techniques, such as culturing specimens obtained by catheterization or suprapubic aspiration. Failure to identify an organism does not preclude it.

Proper manual microscopy of the urine using a haemocytometer should form part of a definitive work-up, although this is rarely deployed. Most laboratories nowadays screen urine in wells using inverted microscopes or rely on robotic detection of pyuria, both of which are insensitive. This is regrettable since studies have shown that significant pyuria is a nearly universal indicator of urinary tract infection, although it is not specific for differentiating cystitis from urethritis, particularly urethritis due to *Chlamydia trachomatis*. In relation to the latter, dysuria also merits the microscopic examination of a urethral smear after it has been Gram stained. If present, a purulent urethral exudate will be very evident, although identification of a causative microorganism will be achieved in less than 50% of cases. The expression 'non-specific urethritis' is apposite and honestly states our current ignorance.

Urethral trauma arising from intercourse may cause pain and dysuria. This used to be called 'honeymoon cystitis', and friction and trauma to the urethra may be the cause in the absence of infection. Women with pelvic floor dysfunction sometimes describe the symptoms, as do postmenopausal women in whom the trauma is associated with oestrogen deficiency, loss of lubrication and vaginal dryness.

Unless a thorough assessment is carried out, bearing in mind the comments described above, the diagnosis of urethral syndrome does not seem credible. There are no data available to answer the inevitable question 'How common is dysuria in the presence of negative rigorous investigation of the bladder and urethra?' Furthermore, the outcome figures for the antibiotic treatment of culture-negative dysuria are unknown.

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6. PELVIC PAIN IN GYNAECOLOGICAL PRACTICE

6.1 Introduction

The approach to pelvic pain presenting to the gynaecologist relies upon the same priciples, namely to illucidate remediable causes and treat them by the most effective therapies in current use. This will then leave 30% (1)

for which no cause can be found; these patients provide the greatest therapeutic challenge.

6.2 Clinical history

A detailed medical history is an essential starting point because the nature, frequency and site of the pain, as well as its relationship to precipitating factors and the menstrual cycle, may provide vital clues to the aetiology.

A detailed menstrual and sexual history, including any history of sexually transmitted diseases and vaginal discharge is mandatory. Discrete inquiry about previous sexual trauma may be appropriate.

6.3 Clinical examination

Abdominal and pelvic examination will exclude any gross pelvic pathology (tumours, scarring and reduced uterine mobility), as well as demonstrating the site of tenderness if present. Abnormalities in muscle function should also be sought.

6.3.1 Investigations

Vaginal and endocervical swabs to exclude infection are mandatory, cervical cytology screening is advisable.

Pelvic ultrasound scanning provides further information with regard to pelvic anatomy and pathology.

Laparoscopy is the most useful invasive investigation to exclude gynaecological pathology (2) and to assist in the differential diagnosis (3).

6.4 Dysmenorrhoea

Pain in association with menstruation may be primary or secondary.

Primary dysmenorrhoea classically commences with the onset of ovulatory menstrual cycles and tends to decrease following childbirth (4).

Explanation and reassurance may be helpful, together with the use of simple analgesics progressing to the use of non-steroidal anti-inflammatory drugs (NSAIDs), which are particularly helpful if they are started before the onset of menstruation. The efficacy of NSAIDs in this condition is probably related to the effects on prostaglandin synthetase. Suppression of ovulation using the oral contraceptive pill reduces dysmenorrhoea dramatically in most cases and may be used as a therapeutic test. Because of the chronic nature of the condition, potentially addictive analgesics should be avoided.

Secondary dysmenorrhoea would suggest the development of a pathological process, and the exclusion of endometriosis (5) and pelvic infection is essential.

6.5 Infection

A history of possible exposure to infection should be sought and it is mandatory in all cases to obtain swabs to exclude chlamydia and gonorrhoea, as well as vaginal and genital tract pathogens (6). Patient's sexual contacts will need to be traced in all cases with positive cultures. If there is doubt about the diagnosis then laparoscopy may be of great assistance.

Primary herpes simplex infection may present with severe pain (7) associated with an ulcerating lesion and inflammation, which may lead to urinary retention (8) and require hospitalization and the use of opiates to achieve adequate analgesia.

6.5.1 Treatment

The treatment of infection depends on the causative organisms. Subclinical chlamydial infection may lead to tubal pathology. Screening for this organism in sexually active young women may reduce the incidence of subsequent subfertility.

Chronic pelvic inflammatory disease is no longer common in developed countries, but still poses a significant problem with chronic pain in the Third World.

6.6 Endometriosis

The incidence of endometriosis is rising in the developed world. The precise aetiology is still a source of debate, but an association with nulliparity is well accepted.

The condition may be suspected from a history of secondary dysmenorrhoea and often dyspareunia, as well as the finding of scarring in the vaginal fornices on vaginal examination, with reduced uterine mobility and adnexal masses. The most useful diagnostic tool is the laparoscope (9,10).

Endometriotic lesions affecting the urinary bladder or causing ureteric obstructions can occur, as well as lesions affecting the bowel, which may lead to rectal bleeding in association with menstruation.

6.6.1 Treatment

Analgesics and NSAIDs are helpful in ameliorating the pain at the time of menstruation, as in primary dysmenorrhoea. Hormone treatment with progestogens or the oral contraceptive pill may halt the progress of

the condition, but are not curative. Luteinizing hormone releasing hormone (LHRH) analogues to create an artificial menopause will give a temporary respite, but with marked side effects due to the oestrogen deficiency. These drugs are used in preparation for surgery to improve surgical outcome and reduce surgical complications.

Surgery for endometriosis is challenging, the extensive removal of all endometriotic lesions is essential. The best results are achieved laparoscopically, by highly trained and skilled laparoscopic surgeons, in specialist centres (11). A multidisciplinary team will be required for the treatment of extensive disease, including a pain management team.

The pain associated with endometriosis is often not proportionate to the extent of the condition and, even after extensive removal of the lesions and suppression of the condition, the pain may continue.

6.7 Gynaecological malignancy

The spread of gynaecological malignancy of the cervix, uterine body or ovary will lead to pelvic pain depending on the site of spread. Treatment is of the primary condition, but all physicians dealing with pelvic pain must be fully aware of the possibility of gynaecological malignancy.

6.8 Injuries related to childbirth

Tissue trauma and soft tissue injuries occurring at the time of childbirth may lead to chronic pelvic pain related to the site of injury. Dyspareunia is a common problem leading to long-term difficulties with intercourse and female sexual dysfunction (12). Denervation of the pelvic floor with re-innervation may also lead to dysfunction and pain.

Vulvar pain and psychosexual problems are discussed extensively in other sections of this text.

Postmenopausal oestrogen deficiency may lead to pain associated with intercourse, which will respond to hormone replacement therapy.

6.9 Conclusion

Once all the above conditions have been excluded, the gynaecologist may well be left with patients with unexplained pelvic pain. It is, of course, imperative to consider pain associated with the urinary and gastrointestinal tract at the same time. An example of this is that it is not uncommon to find patients with bladder pain, presenting with dyspareunia, due to bladder base tenderness.

Previously pelvic congestion was cited as a course of pelvic pain of unknown aetiology but this diagnosis is not universally recognised (13,14).

As previously stated in dealing with pelvic pain a multidisciplinary approach taking into consideration all possible causes, will yield the best results.

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7. NEUROLOGICAL ASPECTS

7.1 Introduction

It is clearly important for the patient to have been thoroughly examined by a urologist or gynaecologist and local pelvic pathology excluded. Once a structural cause has been eliminated, a neurological opinion is often sought and, again, the prime aim of the neurologist must be to exclude any form of conus or sacral root pathology. MRI is the investigation of choice to show both neural tissue and surrounding structures.

If all examinations and investigations fail to reveal an abnormality, the diagnosis is likely to be one of the focal pain syndromes. These are chronic persistent, or recurrent or episodic pains referred to specific pelvic organs in the proven absence of infection, malignancy or other obvious pathology (see Table 1). These are well-recognized conditions, but their pathophysiology is not understood. However, it seems likely that the problems relate in some way to the combined visceral, autonomic and somatic innervation of the pelvic organs.

7.2 Pudendal nerve entrapment

Chronic compression of the pudendal nerve in the ischiorectal fossa may result in a perineal pain located either anteriorly in the vagina or vulval region, or posteriorly in the anorectal region. The ICS has used the following definition “Perineal pain is felt: in the female, between the posterior fourchette (posterior lip of the introitus) and the anus, and in the male, between the scrotum and the anus” (1).

The pain may include unpleasant sensations of numbness or a burning sensation, and may be exacerbated by sitting and relieved by standing. Neurological examination of the perineum is normal and, if tested, the sacral reflexes are present and anal sphincter tone normal. Neurophysiological examination is said to be helpful is some cases; use of the sacral reflex latency (using electrical stimulation of the dorsal nerve of the clitoris and recording muscle activity in the perineum) and the pudendal nerve distal motor latency using the St Marks Stimulator has been recommended. These investigations require specialist neurophysiological expertise.

Despite these claims, the reality is that pudendal nerve neuropathy is probably only a likely diagnosis if the pain is unilateral, has a burning quality and is exacerbated by unilateral rectal palpation of the ischial spine, and the pudendal motor latency is delayed on that side only. However, such cases account for only a small

proportion of all those presenting with perineal pain and the proof of the diagnosis resting on relief of pain following decompression of the nerve in Alcock's canal is rarely achieved. The value of the clinical neurophysiological investigations is debatable; some centres in Europe claim that the investigations have great sensitivity (1,2), while other centres, which also have a specialized interest in pelvic floor neurophysiology, have not positively identified any cases. Further information may be gained by a diagnostic nerve block or MRI investigation.

7.3 Other neurogenic conditions

Other pelvic floor clinical neurophysiological investigations are more helpful in identifying changes of denervation and reinnervation, and lesions causing such disorders are usually associated with bladder and/or sexual dysfunction rather than isolated urogenital pain.

A major defect of the clinical neurophysiological investigations currently available is that they examine mostly large myelinated nerve fibre function, rather than the unmyelinated and small myelinated fibres, which subserve autonomic innervation, pelvic organ sensation and pain (3).

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8. PELVIC FLOOR FUNCTION AND DYSFUNCTION

8.1 Introduction

The pelvic floor is made up of muscles and fascia. The muscles usually function as a composite, although the anterior and posterior components may act in isolation. The pelvic floor has three functions: support, contraction and relaxation.

8.2 Function

In its resting state, the pelvic floor supports the bladder and the urethra in the anterior compartment, the uterus and the vagina in the middle compartment and the rectum and the anus in the posterior compartment. The integrity of the support function depends on the anatomical position of the muscles, on the resting 'tone' and on the integrity of the fascia (1). Like all skeletal muscles, tone is maintained by the efferent nerve fibres, and may vary with hormonal status (menstrual cycle, pregnancy, and menopause).

The support activated during a rise in intra-abdominal pressure is different from that at rest. When intra-abdominal pressure rises, the pelvic floor muscles must respond with a contraction occurring simultaneously or before the pressure rise. The latter is termed an anticipatory 'response' or feed-forward loop (2). Electromyography (EMG) recordings show tonic motor unit activity at rest, with phasic recruitment of large motor units in response to coughing.

A contraction of the pelvic floor muscles results in an inward movement of the perineum and an upward movement of the pelvic organs. In many situations, other muscles such as the abdominal muscles, the adductor muscles and the gluteal muscles are also contracting. There are two types of contraction that can be distinguished: a voluntary contraction resulting from impulses arising in the cerebral cortex; and a reflex contraction. These contractions not only maintain support of the pelvic organs, they close the urethra, anus and vagina, thus avoiding loss of urine or stool, and affording women a defensive mechanism. Additionally, detrusor inhibition occurs in parallel with pelvic floor muscle contraction.

A contraction of the pelvic floor muscles must have sufficient strength. Strength results from muscle capacity and neurogenic drive, reflected in the frequency of excitation and the number of activated motor units. Increase of muscle strength is achieved through the recruitment of more motor units. A contraction must be

rapidly effective and remain so for a certain period (endurance).

Contractions of the pelvic floor play an important role in sexual function. During the arousal phase, pelvic floor muscle contractions are used to increase vasocongestion. During the last phase of the sexual response cycle, a series of involuntary contractions is associated with the physical sensations of orgasm (3).

Pelvic floor muscle relaxation results in a decrease or termination of the squeezing of the urethra, vagina and anus. The perineum and the pelvic organs return to their anatomical resting position. Pelvic floor muscle relaxation is the result of inhibition of tonically active motor units. Relaxation of the pelvic floor muscles is needed for voiding, defaecation and for sexual intercourse.

8.3 Dysfunction

Dysfunction of the pelvic floor can mean overactivity or underactivity. When the pelvic floor is underactive, it means that muscles do not contract when they need to. In practice, this leads to incontinence of urine or stool. It may also diminish the ability to postpone voiding or give rise to pelvic organ prolapse. Overactivity of the pelvic floor means that the pelvic floor muscles do not relax when they should. During voiding and defaecation, the outflow resistance is too high resulting in low flow rates and constipation (4). Another consequence of overactivity is dyspareunia.

Overactivity tends to develop over a protracted period, with the causes proving diverse. Some professions, notably people working in restaurants, cab drivers and school teachers are at increased risk for developing an overactive pelvic floor: They all share the problem of limited access to a toilet on demand. Voiding is postponed by contraction of the pelvic floor muscles. When they do eventually void, detrusor power is lacking. They resort to abdominal straining which results, through the guarding reflex, in contraction of the pelvic muscles (5).

An overactive pelvic floor will cause pain. The mechanism has only partly been elucidated (6). A muscle that is continuously contracting will ache. Nerves and vessels that pass through the pelvic floor may be compressed, as is the pudendal nerve in Alcock's canal, or obstructed as are the vessels to the penis and scrotum. Both mechanisms lead to pelvic pain. A contracting pelvic floor will increase afferent input to the sacral spinal cord, the pons and the cerebral cortex. In response, the central nervous system may modify efferent signals to the pelvis. This change in efferent activity may aggravate the situation further (7).

8.4 Therapy

Treating pelvic floor overactivity should be considered in the management of chronic pelvic pain (8). There are a number of methods, usually taught by physiotherapists, which can be used to improve the function and coordination of this muscle group. In this context, normal function can be restored by coordinating muscle activity with respiration (contract with expiration and relax with inspiration).

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9. PSYCHOLOGICAL FACTORS IN CHRONIC PELVIC PAIN

9.1 Introduction

The function of pain, particularly acute pain, is to demand the cessation of further damage. This is especially true for acute pain. When pain persists after the nociceptive stimulus has ceased or the damage has healed, it loses its function. Chronic non-malignant pelvic pain is an example of purposeless pain, which disrupts daily life. A purely somatic approach is not adequate to understanding this situation. Drawing on the gate control theory of Melzack and Wall (1), modern pain research has shown that the perception of pain is modulated by cognitive and psychological processes, which are an integral part of pain processing.

The IASP states that “Pain is an unpleasant subjective, sensory and emotional experience and each individual learns the application of the word through experiences related to injury in early life” (2). Pain is an experience that is more complex than pure nociception.

9.2 Models of pain

9.2.1 Biomedical model

In the biomedical model, pain is described as a symptom of tissue damage. Nociceptive signals are transmitted to the central nervous system. Pain is a pure sensory input to the brain that signals danger because of damage. Treatment consists of blocking the signals, or repairing the damaged tissue.

9.2.2 Psychodynamic model

In the psychodynamic model, as in the biomedical model, pain is seen as the result of underlying pathology, but the cause is psychological. Pain is the expression of an intrapersonal conflict or emotional trauma. Treatment consists of finding the source and reliving causative events of the past.

9.2.3 Biopsychosocial model

The biopsychosocial model is based on the theory that natural processes occur in a system that includes the soma, psyche and social circumstances of the patient. Items of particular significance in this theory include the biomedical factors of somatic trauma, pain as described by the patient and the sociological impediments of life (3). Psychosocial risk factors, such as fear, focus of attention and negative mood states, play a role in the experience of the pain. Like other emotional experiences, pain has three ways to express itself.

9.2.4 Motoric pain behaviour

Pain behaviour is important because it is a means of communication. Demonstrating pain has positive consequences, such as avoiding the imperatives of work, and thereby diminishing pain. A partner or caregiver may pay more attention to the victim when pain is communicated. In this context, purposeless interventions such as repeated diagnostic tests and alterations to medication, prevent patients distancing themselves from the pain. This is called operant conditioning, which results in persistence of pain behaviour after resolution of the cause (4).

9.2.5 Cognitive processes

Pain captures the attention strongly, thereby deferring other cognitive activities (5). At the same time, attention to the pain increases the experience of pain. The strength of the attention for the pain depends on the thoughts patients have about the seriousness of the pain. The word “catastrophysing” is used to categorize thinking such as: “Pain is the worst thing that can happen to me” or “The doctor says he couldn’t find anything wrong; maybe he doesn’t want to say how bad the situation is”. Another important cognitive process is called self-efficacy. This term is used to indicate the confidence patients have in their abilities to perform a specific task. It depends on the task in hand. Self-efficacy when asked to relax the pelvic floor muscle can be different from that when asked to contract these muscles. The relationship between self-efficacy and task performance is stronger than between the pain and performance.

9.2.6 Psychophysiological reactivity

In threatening situations, the body is prepared for flight or fight. The muscles are active in this reaction and, if prolonged, this muscle activity will lead to pain. Stress and threatening circumstances explain situations associated with increased muscle activity such as in the pelvic floor. Repetition of stressful situations, even just thoughts of a situation, can lead to a chronic overactivity of the muscles and this overactivity will worsen pain. Electromyography (EMG) of the back muscles while assessing stress factors showed that EMG activity was increased in a group with pain compared with controls (6).

9.3 Chronic pelvic pain in a biopsychosocial model

Pelvic floor overactivity is a major factor contributing to chronic pelvic pain. The dysfunction of the pelvic floor muscles can have different origins:

1. Conditions affecting structures of the pelvic floor (prostatitis, cystitis, proctitis, vulvo-vestibulitis).
2. Behavioural factors (dysfunctional voiding).
3. Traumatic experiences (physical or sexual abuse or affective deprivation).

In most cases, the cycle starts with increased muscle tension. In the last two categories, psychological mechanisms play an important role. Muscle contraction can function as a defence against traumatic events remembered from earlier life. Pelvic floor muscle overactivity will lead to several symptoms including pain. The pain causes anxiety and distress, which aggravates the muscle contraction. When there is a history of abuse, memories of the traumatic experiences may provoke the pain (7). Conversely, the pain may evoke distressing memories. Chronic pelvic pain may be an allegorical method of describing chronic psychological pain and may act as a defence or coping mechanism in the face of painful, emotional memories (8).

9.4 Psychiatric disorders

There is little published on mental disorders and chronic pelvic pain, but some aspects are covered.

9.4.1 Somatoform pain disorders

Somatization and somatoform disorders are characterized by the presence of physical symptoms that are not fully accounted for by a general medical condition, the effect of a substance, or mental disorder, yet suggest the presence of a medical condition and cause clinically significant distress or impairment (9). Somatization is an avoiding coping strategy. Childhood physical abuse is strongly associated with later somatization. Chronic pelvic pain can be one of the symptoms present in somatoform disorders (10).

9.4.2 Depression

Depression is a state of significantly decreased emotional, psychological and social functioning, with neurovegetative symptoms, lasting at least 2 weeks (9). Anger, fear and hopelessness become turned upon the self. Comorbidity of depression and chronic pelvic pain can have a lifetime incidence as high as 65% compared with only 25% in the general female population (11). In a study of 72 patients with chronic pelvic pain, 51% had clinical depression and 72% had sleeping disorders. A subclinical depression is often overlooked and this can worsen or prolong chronic pelvic pain (12). In a study of men, it was concluded that depression and psychosocial distress are common in patients with chronic prostatitis (13).

9.5 Abuse and chronic pelvic pain

Physical and sexual abuse are serious problems, which can happen during childhood, adulthood or both. Many studies have been carried out to elucidate the relationship between chronic pelvic pain and abuse. For a long period, the overall assumption was that sexually abused children or adults would be prone to developing chronic pelvic pain. Current data do not, however, support this, although there are some correlations. There is an association between chronic pelvic pain and major abuse, sexual or physical. Victims of both types of abuse, especially is during childhood, seem particularly at risk of pelvic pain. The greater the magnitude of the abuse, the stronger is the correlation with chronic pelvic pain (14,15). A recent article reported on a prospective investigation into the relationship between abuse and chronic pelvic pain. The conclusions of this study were that physically and sexually abused individuals were not at risk for increased pain symptoms. The relationship between childhood victimization and pain symptoms is less straightforward than previously thought (16). When no reasons for chronic pelvic have been found, it is important to ask about physical and sexual abuse when taking the history, because of the consequences for the therapy chosen. On the other hand, it is important to note that chronic pelvic pain should not be used to stigmatize patients as being abused.

Chronic pelvic pain patients with a history of abuse have higher dissociation and somatization scores on psychological tests. Childhood physical abuse is strongly related to later somatization, as may sexual abuse (17). Dissociation is a way of splitting memories of frightening experiences from consciousness. It is the victim's attempt to escape what is inescapable.

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10. GENERAL TREATMENT OF CHRONIC PELVIC PAIN

10.1 Analgesia

10.1.1 Non-acidic antipyretic analgesics

Paracetamol is the main representative of this group. It has antipyretic activity and is a simple analgesic. There is very little evidence about its role in chronic pelvic pain. Further studies need to be considered (1,2). Paracetamol should be considered for mild pain.

10.1.2 Acidic antipyretic analgesics

The classical NSAIDs fall into this group and include salicylic acid. They are known to act on the cyclooxygenase (COX) enzyme. The early NSAIDs tended to have little selectivity for COX2 over COX1, and are therefore said to be associated with more side effects than the newer, COX2 selective inhibitors. The COX1 enzyme is mainly involved in normal 'housekeeping' functions, such as mediating gastric mucosal integrity, and renal and platelet function. Blocking the COX1 enzyme is the cause of the platelet, gastric and renal complications that can occur with NSAIDs. It has been suggested that the COX2 enzyme is inducible as a result of tissue damage, and that it is the main enzyme involved in inflammation and peripheral sensitization of nociceptors. As a result, the analgesic efficacy of COX2 selective drugs should be as good as that of the non-selective drugs. This, however, has recently been disputed (3-7).

There is very little evidence for a role of NSAIDs in the management of chronic pelvic pain and even less evidence for a role for the COX2 selective drugs. Most of the analgesic studies have investigated dysmenorrhoea in which NSAIDs have been found to be superior to placebo and possibly paracetamol (1,8).

For practical purposes the NSAIDs may be divided into:

1. Non-selective, low potency (e.g. salicylic acid, ibuprofen, mefenamic acid).
2. Non-selective, high potency (e.g. ketoprofen, diclofenac, ketorolac).
3. COX2 selective drugs (e.g. rofecoxib, celecoxib, etoricoxib).

10.1.3 Guidelines for use

Non-selective, low potency NSAIDs should be used in the first instance. They are most likely to be of help if there is an inflammatory component to the pain. More potent NSAIDs should be reserved for those conditions in which the low potency drugs have been tried and failed to produce significant benefit. COX2 selective drugs may be used as an alternative to the non-selective drugs where there is an increased risk of gastric complications, such as in patients over 65 years of age, patients receiving prolonged therapy at high dose, patients taking medications that may also induce gastrointestinal bleeding, or patients with a previous history of gastrointestinal problems. NSAIDs should be taken with food. Consideration must be given to the use of gastric protective agents

The benefits of the NSAIDs must be demonstrated to outweigh the risks. All NSAIDs are contraindicated in active gastrointestinal ulceration/bleeding and renal disease. They may seriously exacerbate asthma and produce fluid retention.

Even if stronger analgesics such as opioids are added, the NSAIDs can be continued as they are likely to have a synergistic action improving pain control above and beyond that obtained with opioids alone (9).

10.1.4 Opioids

There is now a general acceptance that opioids have a role in the management of chronic non-malignant pain (10). The use of opioids in urogenital pain is poorly defined. The following guidelines are suggested.

10.1.5 General guidelines for the use of opioids in chronic/non-acute urogenital pain

1. All other reasonable treatments must have been tried and failed.
2. The decision to instigate long-term opioid therapy should be made by an appropriately trained specialist in consultation with another physician (preferably the patient's family doctor).
3. Where there is a history or suspicion of drug abuse, a psychiatrist or psychologist with an interest in pain management and drug addiction should be involved.
4. The patient should undergo a trial of opioids. This may be an intravenous (10) or oral trial (11).
5. The dose required needs to be calculated by careful titration.
6. The patient should be made aware (and possibly give written consent):
   I. that opioids are strong drugs and associated with addiction and dependency
   II. the opioids will normally only be prescribed from one source (preferably the family doctor)

III. the drugs will be prescribed for fixed periods of time and a new prescription will not be available until the end of that period
IV. the patient will be subjected to spot urine and possibly blood checks to ensure that the drug is being taken as prescribed and that non-prescribed drugs are not being taken
V. inappropriate aggressive behaviour associated with demanding the drug will not be accepted
VI. hospital specialist review will normally occur at least once a year
VII. the patient may be requested to attend a psychiatric/psychology review
VIII. failure to comply with the above may result in the patient being referred to a drug dependency agency and the use of therapeutic, analgesic opioids being stopped.

7. Morphine is the first-line drug, unless there are contraindications to morphine or special indications for another drug. The drug should be prescribed in a slow release/modified release form. Short-acting preparations are undesirable and should be avoided where possible. Parenteral dosing is undesirable and should be avoided where possible.

Morphine. There is no compelling evidence that one opiate is better than another (12). Morphine is the traditional gold standard. In an acute situation, the daily morphine requirement may be calculated by titration of the drug with progressively increasing doses of 4-hourly rapid-release morphine. However, in most cases, starting with a low dose of slow-release morphine and confining the increments to occur at intervals of no less than 3 days to 1 week is adequate.

Diamorphine is not generally available orally, because of its high first-pass metabolism within the liver. It should not be used routinely for long term pain management in patients with chronic/non-acute pain.

A fentanyl patch is used when oral absorption is restricted or when the patient suffers with nausea and vomiting. Patches are generally changed every 72 hours. The problem with the currently available patches is that the dosing increments between patches are large. Care needs to be exercised when increments in dose are undertaken.

Methadone is a strong analgesic which has a long track record (13). It may have a useful role in the management of urogenital pain, though there is very little science to support this. Methadone has the tendency to accumulate with repeated dosing and cause delayed respiratory arrest. Therefore, whereas it may be a very useful drug, it should only be prescribed by a practitioner familiar with its use as an analgesic (11). Methadone as an analgesic is usually prescribed 6 hourly as its analgesic action is relatively short-lived compared with the longer benefits seen from using the drug in drug addiction.

Pethidine 100 mg i.m. is about as effective as tramadol 100 mg i.m. (14) or morphine 10 mg i.m. Its oral bioavailability is, however, poor. Pethidine has a short duration of action and is therefore not an ideal drug for use in chronic/non-acute pain. Frequent administration may result in the accumulation of norpethidine, which is associated with a tendency to epileptic seizures (15,16). Serious drug interactions can occur in patients taking pethidine with selective and non-selective monoamine-oxidase inhibitors, or serotonin reuptake inhibitors. The result may be cerebral excitation and hyperpyrexia. Pethidine should not be used routinely in non-acute/chronic pain (17).

Other opioids. Oxycodone and hydromorphone are now both available as slow/modified-release preparations. They may be useful for opiate rotation if side effects or tolerance is a problem. They are powerful opioids. Phenazocine is effective in severe pain. It may be administered sublingually if nausea and vomiting are a problem.

Buprenorphine and pentazocine both have agonist and antagonist properties and can induce withdrawal symptoms in patients used to opioids. Naloxone may only partly reverse respiratory depression. Buprenorphine topical patches are now available.

Codeine and dihydrocodeine are effective for the relief of mild-to-moderate pain. However, dihydrocodeine is a drug that is frequently abused.

10.1.6 Opioid-like agents

Tramadol produces analgesia by two mechanisms: an opioid effect; and an enhancement of serotoninergic and adrenergic pathways (18,19). It has fewer of the typical opioid side effects (notably, less respiratory depression, less constipation and less addiction potential).

10.1.7 Neuropathic analgesics

Tricyclic antidepressants. Once again, there is very little evidence available in humans (20-22). A study in cats does suggest that tricyclics may have a role in the management of cystitis (23). Most of the studies involve neuropathic pain. If there is a suggestion of nerve injury or central sensitization, the algorithm outlined in Figure 4 should be considered.

McQuay and Moore (12) reviewed those studies in which tricyclics had been investigated in neuropathic pain. They concluded that tricyclics have a definite analgesic effect compared with placebo: 30% of patients should obtain more than 50% pain relief; 30% will have minor adverse effects; and 4% will have to stop treatment because of side effects. Tricyclics are said to work in doses that are too low to affect mood. They may work by increasing levels of nortriptyline or serotonin. They also have actions at sodium channels.

Serotonin reuptake inhibitors. McQuay and Moore (12) conclude that selective serotonin reuptake inhibitors are less effective for the management of pain. Fluoxetine can increase plasma levels of amitriptyline and induce toxicity, and therefore care must be exercised if the drugs are combined.

Anticonvulsants have been used in the management of pain for many years. Carbamazepine is one of the few effective interventions for trigeminal neuralgia (12). However carbamazepine has significant side effects and is often poorly tolerated. Phenytoin or valproate have been used instead. Gabapentin has recently been introduced for pain management. It is said to have fewer side effects and in certain countries is now licensed for use in chronic neuropathic pain. It is said to produce a more natural sleep state at night than the antidepressants (24,25). Many practitioners would no longer countenance the use of carbamazepine in pain management because of its potentially serious side effects. Carbamazepine has still been left in the guidelines (Figure 5) in view of its low cost.

Whereas there is little evidence to support the use of anticonvulsants in the management of genitourinary pain, they should be considered if there is a suggestion of neuropathic pain or central sensitization (26,27).

N-methyl-D-aspartate (NMDA) antagonists. The NMDA receptor channel complex is known to be an important channel for the development and maintenance of chronic pain. It is felt to be particularly important when there is evidence of central sensitization and opioid tolerance (28).

Ketamine has been used as a general anaesthetic for over 30 years. It has also been used as an intravenous analgesic in burns units, and accident and emergency units. Ketamine is thought to act primarily at the NMDA receptor, though it may also have actions at sodium channels, as well as opioid (kappa and mu) receptors (29).

Ketamine has been shown in both human and animal models of neuropathic pain to reduce central sensitization and wind-up (29-31). These are the phenomena that alter signal transmission within the nervous system so that non-painful stimuli may become painful (allodynia) and pain from a painful stimulus is magnified (hyperalgesia).

Ketamine has been found to be useful in a number of chronic pain states including: peripheral neuropathies with allodynia, stump and phantom pain, central pain, and cancer-related pain with and without a neurological component (32). Difficult urogenital pains may therefore be helped by ketamine if there is evidence of nerve injury or central sensitization (33-36). Ketamine may be useful in opioid-resistant pain in which it may restore the opioid dose-response curve towards normal (33,37). Ketamine may also be useful in intractable pelvic cancer pain.

Oral ketamine has a bioavailability of about 17%. A test dose given by intravenous infusion is a quick way of establishing whether oral ketamine may be viable (11). Certain chronic pain patients, especially patients with cancer pain, may be sent home with either a subcutaneous or intravenous infusion of ketamine. Ketamine is a street drug of addiction and great care must be exercised if a patient is to be managed at home on parenteral ketamine. Ketamine should only be used by an experienced practitioner trained in its use.

Sodium channel blockade. In a significant number of patients with urogenital pain, nerve injury and neuropathic changes are thought to play a role. These may be associated with a reduction of some sodium channels and the development of novel sodium channels. There is also a change in the distribution of these channels (cell body, dendrites and tips of injured axons). The consequences of these changes are that injured afferents become prone to generating more prolonged and higher frequency discharges. The refractory period is reduced. These changes in the characteristics of sodium channels are thought to underlie the mechanisms of mechanosensitivity, thermosensitivity and chemosensitivity (38). They may be involved in some of the visceral hyperalgesias.

In animal models of neuropathic pain, low doses of the sodium channel blocker lidocaine, have been demonstrated to reduce spontaneous neuronal firing in a selective manner that does not block normal axonal

firing (39,40). Human studies have demonstrated that low plasma doses of lidocaine reduce neuropathic pain and sensory phenomena, such as allodynia, without any effect on nociceptive pain (41). Nociceptive pain may be reduced with intravenous lidocaine, but only with high doses.

A positive lidocaine challenge may be followed by repeated infusions of lidocaine. Benefit from a single infusion may last for many months. A role for the oral analogue, mexiletine, may also be defined (42), though, a positive response to intravenous lidocaine does not always indicate that mexiletine will work.

An intravenous lidocaine trial is indicated in patients with neuropathic pain and pain in which there is a suggestion of central sensitization, such as some of the visceral pains with referred muscle hyperalgesia and cutaneous hypersensitivity (43-45). Details of the protocols for intravenous lidocaine infusions can be obtained from the literature (11). Infusions should only be performed by practitioners trained in the appropriate skill. Examples of infusions used are:

1. The bolus regimen - lidocaine 1 mg/kg given as a slow bolus over 3 minutes and then repeated after 15 minutes up to three times (a maximum of 4 mg/kg over 60 minutes).
2. Short infusion regimen - lidocaine 3 mg/kg over 1 hour using an infusion pump.
3. 4-hour infusion - lidocaine 2 mg/kg over 4 hours by infusion pump.

Figure 4

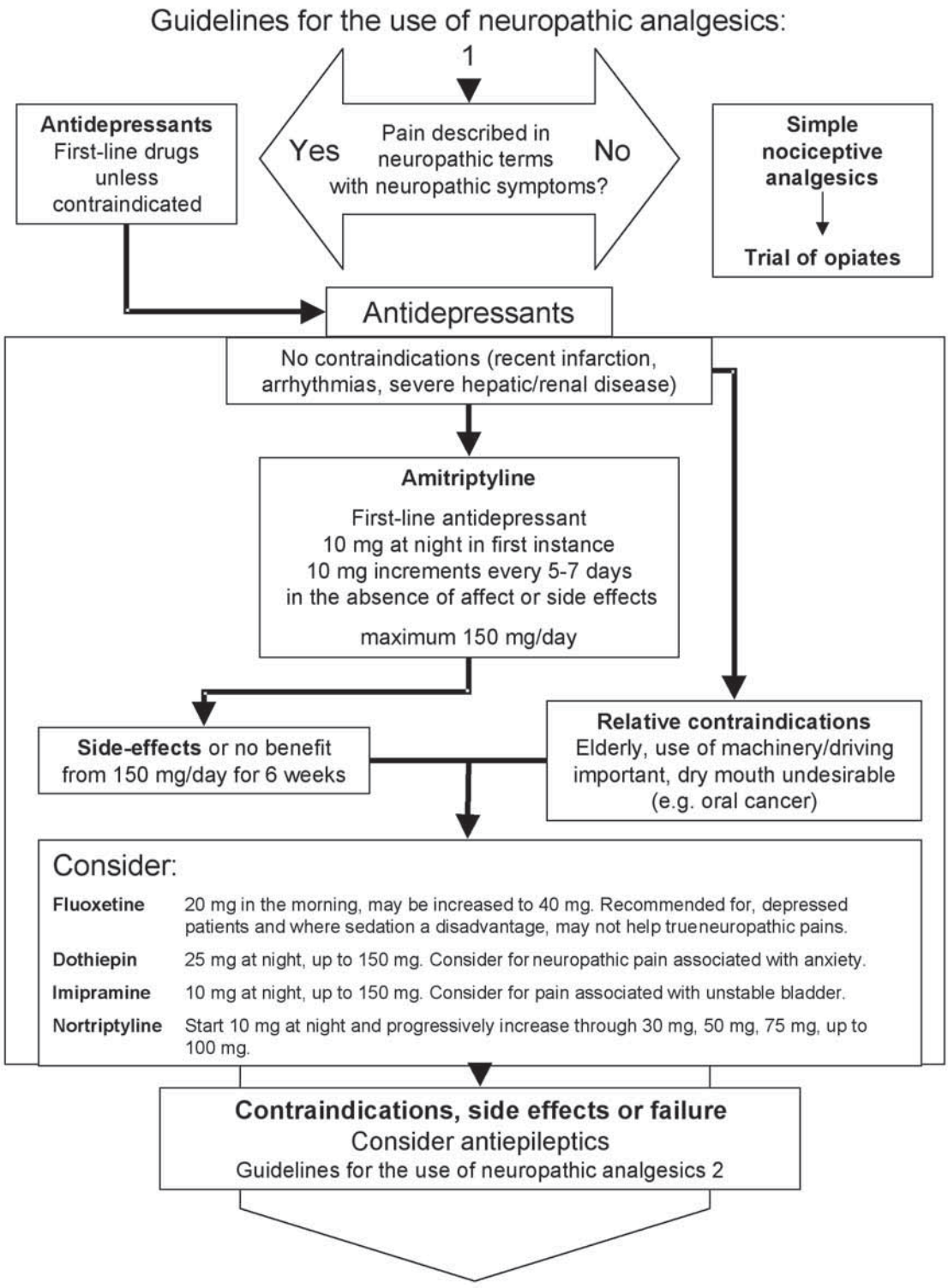
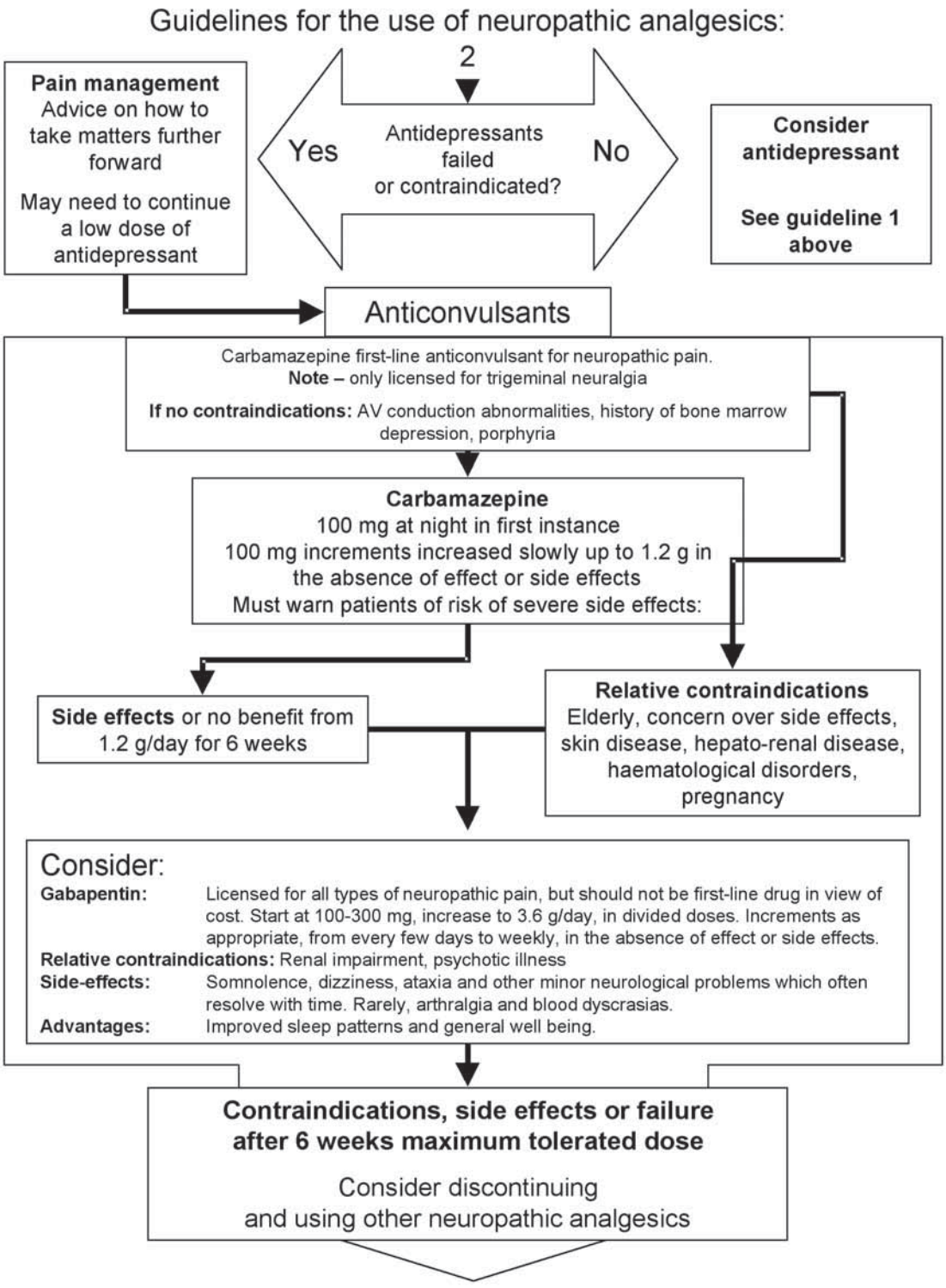

Guidelines for the use of neuropathic analgesics:
1
Antidepressants
First-line drugs
unless
contraindicated
Yes
Pain described in
neuropathic terms
with neuropathic symptoms?
No
Simple
nociceptive
analgesics
Trial of opiates
Antidepressants
No contraindications (recent infarction,
arrhythmias, severe hepatic/renal disease)
Amitriptyline
First-line antidepressant
10 mg at night in first instance
10 mg increments every 5-7 days
in the absence of affect or side effects
maximum 150 mg/day
Side-effects or no benefit
from 150 mg/day for 6 weeks
Relative contraindications
Elderly, use of machinery/driving
important, dry mouth undesirable
(e.g. oral cancer)
Consider:
Fluoxetine
20 mg in the morning, may be increased to 40 mg. Recommended for, depressed patients and where sedation a disadvantage, may not help trueneuropathic pains.
Dothiepin
25 mg at night, up to 150 mg. Consider for neuropathic pain associated with anxiety.
Imipramine
10 mg at night, up to 150 mg. Consider for pain associated with unstable bladder.
Nortriptyline
Start 10 mg at night and progressively increase through 30 mg, 50 mg, 75 mg, up to 100 mg.
Contraindications, side effects or failure
Consider antiepileptics
Guidelines for the use of neuropathic analgesics 2

Figure 5



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10.3 Nerve blocks

The domain of neural blockade for pain management usually lies with the Consultant in Pain Medicine with an anaesthetic background. Whole texts have been written on the techniques employed. Individual specialists involved in neural blockade must be well versed in the assessment of the patient, the indications for specific procedures, and the general and specific risks associated with the procedures, as well as possible advantages.

Procedures may be performed for diagnostic reasons, therapeutic benefit or possibly both. Diagnostic blocks can be difficult to interpret and a clear understanding of the multiple mechanisms by which a block may work must be understood. Temporary but consistent responses to nerve blocks may lead a specialist to proceed with a neurolytic block. However, neurolytic blocks are rarely indicated for a benign process, and to proceed with one may produce disastrous results. The evidence is not strong (1-5), but suggests that:

1. Peripheral nerve blocks, such as ilioinguinal/iliohypogastric/genitofemoral, may be useful in neuropathic pain associated with nerve damage, such as following hernia repairs.
2. Blocks around the spermatic cord may be useful diagnostically prior to testicular denervation.
3. Lumbar (L1) sympathetic blocks may be helpful in the management of testicular pain and possibly other pelvic conditions with afferents passing to the L1 level.
4. Pudendal nerve blocks may be useful in the management of pudendal nerve injury and possibly pelvic floor muscle spasm.
5. Pre-sacral blocks may have a role in the management of pelvic pathology, particularly cancer pain.
6. Sacral root nerve blocks may be helpful in the diagnosis of those conditions that might respond to sacral root stimulation.

10.4 Transcutaneous electrical nerve stimulation (TENS)

The rationale of surface electrical nerve stimulation to relieve pain is the stimulation of myelinated afferents and thereby the activation of segmental inhibitory circuits. Urinary frequency may also be reduced. The favoured explanation of TENS draws on the gate-control theory (6). Nevertheless, TENS may directly elicit reflex effects and influence autonomous functions. For example, relaxation of the bronchial muscles (7), the coronary arteries (8) and the urinary bladder have been observed in response to TENS (9).

TENS involves the use of a pulse generator with amplifier and electrodes. The pulses may be delivered continuously or as trains of varying duration. Continuous stimulation seems to be preferable when treating pain. The stimulation pulses may have different properties. Square-wave pulses, being notably effective in activating the nerve fibres, are most frequently used. Biphasic pulses are preferable since the zero net charge flow of this pulse helps to reduce electrochemical reactions at the electrode contact sites. Nevertheless, technical simplification has led to the use of unipolar rectangular pulses in many devices, apparently with few complications. The stimulus intensity required to activate a peripheral nerve varies with the pulse duration. In terms of charge transfer for a threshold effect, short pulses (0.1 ms) are most effective, but at the expense of higher pulse amplitudes (10). For most applications of nerve stimulation, the pulse frequency is a crucial variable. The frequencies used during TENS vary widely, from 1 Hz to 100 Hz. There are no systematic evaluation data to guide optimal electrical settings for TENS in urological practice.

Standard electrodes are made of carbon rubber. These are strong, flexible, durable and cheap, but must be attached by adhesive tape. Self-adhesive electrodes have been developed. These are especially advantageous for people with sensitive skin, but they are expensive. The size of the electrode has a bearing on the current density — a minimum of 4 cm^2 has been recommended for TENS (11). The electrode-skin impedance should be reduced by application of a generous layer of electrolyte gel to promote good contact under the entire electrode.

The stimulus intensity required to elicit sensory appreciation varies between individuals. The maximum tolerable intensity just below pain threshold should be used. While it is plausible that electrode positioning will affect the result of treatment, this property has not been evaluated. In IC, suprapubic (12,13), vaginal-anal (9,14) and tibial nerve sites (15,16) have been tested, all with some success.

Counselling of the patient before the start of the treatment is necessary. A specially trained nurse with the time necessary to communicate the technical instructions is a good option. The patient should be confident with the feeling of strong stimulation and view self-treatment without fear. The induction time for TENS to produce analgesia varies widely. The effect is cumulative. Since onset and progression are usually rather slow in IC, the standard recommendation so far has been 0.5-2 hours treatment twice daily. The duration of an individual treatment session depends on the severity of pain.

10.4.1 Results of suprapubic TENS in IC

Sixty patients, 33 with classic IC and 27 with non-ulcer disease, were treated by suprapubic TENS (11). The electrodes were positioned 10-15 cm apart immediately above the pubic symphysis. They were attached by a long strip of adhesive tape going half way round the body to enable the patient to be ambulant during stimulation. Follow-up ranged from 9 months to 17 years.

Patients who responded reported more marked effects on bladder pain than on micturition frequency. Nine patients with classic IC had remission of symptoms after treatment of more than 1 year. However, all but one of these patients had to use the devices intermittently to stay free of symptoms.

Another nine patients experienced adequate pain relief with daily treatments, but could not stop TENS without recurrence of symptoms. Nine patients had only a moderate palliation and abandoned the treatment. The remaining six patients reported no symptom improvement at all. Thus, 54% of the patients with classic IC

were helped by the treatment.

The outcome of TENS was less favourable in non-ulcer IC. Of 27 patients (mean age at diagnosis 37 years, one male), four reported remission of pain and urinary frequency and three adequate pain palliation, but persistent voiding frequency during continuing TENS. Five had moderate effect and 15 no pain relief at all. Thus, only 26% of the patients with non-ulcer IC benefited from the treatment.

The present experience of electrical stimulation in IC is based on open studies and patients. There are difficulties in designing controlled studies of TENS, since the treatment is based on administration of stimulation of high intensity, at specific sites, over a very long period of time. It is not possible to measure pain precisely. Therefore, it is difficult to assess the efficacy of TENS in IC with accuracy. A number of controlled studies of postoperative pain have shown TENS to be superior to sham stimulation (17). TENS has been shown to reduce the amount of halothane required to maintain adequate anaesthesia during hand surgery in unconscious patients in whom psychological influences have been eliminated (18). The beneficial effect of TENS on classic IC clearly exceeds the level of the placebo effect observed in drug studies of IC (54% versus 13-20%) (19,20).

10.5 Sacral neuromodulation in pelvic pain syndromes

Sacral neuromodulation has been shown to have benefits in patients with refractory motor urge incontinence (21,22), urinary retention, and chronic pelvic pain (23-25). Neuropathic pain and complex regional pain syndromes may also be treated successfully with neurostimulation applied to dorsal columns and peripheral nerves (26). The mechanisms of action are the subject of hypotheses which include:

1. blocking of pain transmission by direct effects in the spinothalamic tracts
2. activation of descending inhibitory pathways
3. effects on central sympathetic systems
4. segmental inhibition through coarse fibre activation and brain stem loops
5. inhibition by increasing gamma-aminobutyric acid levels in the dorsal horn
6. thalamocortical mechanisms masking the nociceptive input (26,27).

It must be emphasized that the body of experimental data supporting any particular hypothetical mechanism is sparse.

Sacral root neuromodulation was introduced in the mid-1980s as a means of regaining bladder control in the face of disturbed function (28). Based on the neurophysiology of the bladder and urethra, it is a minimally invasive tool that bridges the gap between conservative options and invasive surgical procedures. The data on clinical applications are drawn exclusively from observational studies.

Sacral root neuromodulation draws on the observation that electrical stimulation of sacral nerves modulates neural reflexes of the pelvis (29). Acceptable application of the stimuli is the challenge. Neurostimulation of S3 or S4 sacral nerves using a transforamenal approach is emerging as a viable option for patients with refractory urinary voiding disorders.

Recently, sacral neuromodulation has also been investigated in IC. In an initial report on six patients (30), percutaneous neurostimulation significantly improved frequency, pain and urgency towards normal values, while urinary markers for IC were normalized. Maher et al. (31) reported a favourable response with significant improvement in pelvic pain, daytime frequency, nocturia, urgency and voided volume in 15 women with IC.

Because pelvic pain syndromes are viewed as a manifestation of disturbed neural function, patients with refractory pelvic floor dysfunction and pelvic pain have been treated with sacral neuromodulation and benefit has been reported (32). Sacral neuromodulation for chronic pelvic pain is the beneficiary of promising data from pilot studies, such that prospective, placebo-controlled studies are justified.

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11. LIST OF ABBREVIATIONS

This list is not comprehensive for the most common abbreviations

ABP	Acute bacterial prostatitis
BCG	Bacillus Calmette-Guérin
CBP	Chronic bacterial prostatitis
CFU	Colony-forming units
COX	Cyclooxygenase
CPP(S)	Chronic pelvic pain (syndrome)
CPSI	Chronic Prostatitis Symptom Index
DMSO	Dimethyl sulphoxide
EMDA	Electromotive drug administration
EMG	Electromyography
EPS	Expressed prostatic secretions
GAG	Glycosaminoglycan
GI	Gastrointestinal
GPSS	Giessen Prostatitis Symptom Score
IASP	International Association for the Study of Pain
IC	Interstitial cystitis
ICA	Interstitial Cystitis Association
ICDB	Interstitial Cystitis Data Base
ICS	International Continence Society
IL	Interleukin
IPSS	International Prostate Symptom Score
ISSVD	International Society for the Study of Vulvovaginal Disease
Nd-YAG	Neodymium-yttrium-aluminium-garnet
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
NMDA	N-methyl-D-aspartate
NSAID	Non-steroidal anti-inflammatory drugs
PCR	Polymerase chain reaction
PMN	Polymorphonuclear
PPS	Pentosanpolysulphate
PUGO	IASP special interest group, Pain of Urogenital Origin
RTX	Resiniferatoxin
SPIN	Specialists in Pain International Network
TENS	Transcutaneous electrical nerve stimulation
TUR	Transurethral resection
VB3	Post-prostatic massage urine
WBC	White blood cells