Genitourinary Pain and Inflammation

Diagnosis and Management

Edited by

Jeannette M. Potts, MD

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Genitourinary Pain and Inflammation

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To my patients

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Preface

Any physician who sees men or women for signs or symptoms presenting below the umbilicus would appreciate this comprehensive text in which multiple subspecialists share their perspective with respect to organ-specific disorders as well as the myriad overlapping syndromes that may manifest as genitourinary (GU) inflammation or pain.

Unlike other fields, the subspecialty of pain, particularly genitourinary or pelvic pain, suffers from the lack of objective data and the paucity of level 1 evidence-based studies. I recall an article about fibromyalgia read many years ago, in which the author stated, "the lack of level 1 evidence places a premium on the physician's creativity."

Genitourinary Pain and Inflammation: Diagnosis and Management is a compilation of expert creativity and opinion based on critical review of the literature, consensus reports, and the authors' professional experiences. Inflammation and pain caused by infectious etiologies are presented by experts in urological and gastrointestinal fields. Pain syndromes specific to the pelvic floor or genitourinary system are discussed from several perspectives: gynecology, rheumatology, urology, physical medicine, and psychiatry. We also include chapters addressing iatrogenic causes of GU inflammation, such as those caused by catheters, prosthetics, radiation, or chemotherapy. Management by means of pharmacological, surgical, or alternative methods is likewise considered within the context of specific disease entities, as well as within the separate therapeutic chapters.

In this era of evidence-based medicine, authors needed to confront the ironic lack of level 1 studies in their respective fields. Indeed, the very nature of genitourinary pain may hinder this type of research, which is otherwise feasible for other diseases in which inclusion criteria and outcome measures are defined more objectively. This observation is both the reason and the inspiration for this textbook, the first of its kind.

Pain of any kind causes significant physical and mental disability. But the impact of such discomfort when it affects the pelvis or urogenital tract is tremendously magnified. Depression and desperation experienced as a consequence or as part of the pain syndrome impacts healthcare providers as well. This is especially true in the case of patients suffering from chronic pain. Often, attempts to find the cause are futile, leading to many invasive and unnecessary tests. Out of frustration, physicians may prescribe empiric therapies based on little evidence. Even worse, physicians compelled to "do something" for the patient can potentially cause more harm.

Many of these conditions overlap and might represent a more global or systemic diagnosis consistent with functional somatic syndromes. Recognition of this tendency of shared characteristics among patients and the increased prevalence of functional somatic syndromes observed in my own pelvic pain clinic has also been a significant motivation for this publication.

Our current medical environment limits the quality of the physician–patient relationship due to economic constraints and the reliance on more seductive technology. Yet, it is this relationship and the art of medicine that are most important for the evaluation and treatment of these patients.

Despite the high prevalence of pelvic and genital pain syndromes, frustration and avoidance abound among medical professionals. For this reason, we have compiled a host of expert reviews from all specialty areas involving male and female pelvic regional pain syndromes. The interrelationship of urological, colorectal, and gynecological pathophysiology is demonstrated in addition to the intricacies of biopsychosocial factors.

Dermatological disorders as well as rheumatological considerations are addressed in various sections. Chapters describing the neurophysiology of pain and corresponding pharmacologic interventions are also included.

The book is divided into sections corresponding to conventional diagnostic trends; however, each section contains chapters that address the diagnoses from different disciplinary perspectives.

Genitourinary Pain and Inflammation: Diagnosis and Management would not have been possible without the contributions and active support of the distinguished authors, who have shared their time and expertise. I thank them for their work and for their patience during the development of this book. We hope that our efforts help improve outcomes for your patients.

Jeannette M. Potts, MD

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Color Plates

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I Genitourinary Pain Syndromes Affecting Both Sexes

1 The Neurobiology of Chronic Pelvic Pain

Jennifer Gunter, MD

Summary

Chronic pelvic pain is a response of the nervous system to somatic and visceral pathology. Involving multiple pain pathways, it is unlikely to be confined to one organ system or to one mechanism. An understanding of the complex neuroanatomy and pathophysiologic mechanisms is essential to the treatment of patients presenting with this disorder.

Key Words: Chronic pelvic pain; neuroanatomy; nocioception; neuropathic pain; hyperalgia; neuroinflammatory peptides; gonadal hormones; wind-up response.

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INTRODUCTION

Chronic pelvic pain is not just a symptom it is a disease unto itself. It is the result of multiple pathophysiologic responses that develop in somatic and visceral structures and the corresponding pathologic excitatory processes in both the central and the peripheral nervous systems. Traditional approaches to this challenging medical problem have addressed diagnosis and treatment primarily from a disease-based model (endometriosis, interstitial cystitis, etc.) and largely ignored the role of the nervous system. The response of the nervous system to somatic and visceral pathology is,

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however, the most important concept in the genesis and maintenance of chronic pelvic pain. This chapter will discuss the neurophysiology of pain, review the neuroanatomy of the pelvis, describe the mechanisms involved in the genesis and maintenance of chronic pelvic pain, and explore how these processes relate to some of the traditional pathologies associated with chronic pelvic pain.

NEUROPHYSIOLOGY OF ACUTE PAIN

Pain Pathways

Acute pain is an essential adaptive response of the nervous system to alert the body to pathologic processes or injury. Without pain an inflamed appendix could rupture resulting in sepsis and death or a burn would not be recognized resulting in extensive local injury. Somatic and visceral pain are generated by peripheral nociceptors, undifferentiated nerve endings on the peripheral terminals of primary afferent myelinated AΔ and unmyelinated C-fibers that depolarize in response to various mechanical, chemical, and thermal stimuli *(1,2)*. Somatic pain is transmitted along sensory nerves, and in the pelvis, visceral pain is transmitted through sympathetic fibers. The cell bodies of both the somatic and visceral afferent neurons are in the dorsal root ganglion with a central projection that synapses with second-order neurons in the dorsal horn of the spinal cord. Neuropathic pain is the result of a primary lesion or dysfunction of the nervous system that produces spontaneous neuronal activity.

Nociceptive Mechanisms

Mechanical stimulation or algesic substances, such as histamine and K+ released during tissue injury or inflammation activate the peripheral nocioceptor terminal on somatic nerves causing an influx of sodium across the NA+/K+ channels of the cell membrane *(1,3,4)*. Some nocioceptors are silent, meaning that a very high threshold of stimulation is required before depolarization. When more Na+ is flowing into the cell than K+ out, the cell depolarizes converting the physical/chemical stimulus into an electrical impulse in a process known as transduction *(1,3)*. The wave of depolarization is transmitted along the afferent neuron resulting in the central release of excitatory neurotransmitters, such as glutamate, activating several classes of second-order neurons, primarily in lamina I, II, and V of the dorsal horn *(3,6)*. These post-synaptic neurons cross to the contralateral side of the spinal cord transmitting the painful signal to the brain through the spinothalamic tract. Different types of painful stimuli and different sources of pain, specifically somatic and visceral, activate different cortical regions *(7)*. Once an acute event is registered in the brain, descending modulatory impulses decrease the input to the central nervous system (CNS) by activating inhibitory in the dorsal horn and other mechanisms *(1,5)*.

The sympathetic nerves provide the sensory input from the genitourinary and gastrointestinal tracts *(7,12)*. Stimuli that would elicit a painful response from somatic structures, such as cutting, crushing, and burning, elicit little response from the viscera; however, distention, traction, ischemia, and inflammation provoke a visceral nociceptive response *(6,7)*. Some viscera such as the uterus and ureters have nocioceptors that respond to specific stimuli while others, such as the bladder and colon, respond primarily to the intensity of the stimuli *(7,13–15)*. The silent nocioceptors, a third category, are normally unresponsive but can be stimulated by prolonged noxious

stimuli, resulting in an increased pain response and a heightened response to previous low-threshold stimuli; this phenomenon has been well described in the bladder in response to experimental inflammation *(7,16,17)*. Therefore, the pelvic viscera contain three categories of nocioceptors: stimulus specific, intensity responsive, and silent.

Neuropathic Pain

Neuropathic pain is a primary excitatory disorder of the nervous system and may occur through a variety of mechanisms such as trauma, infection, and ischemia or may occur spontaneously with no apparent etiology. In the pelvis neuropathic pain is most likely the result of surgical injury, other nerve trauma, herpes infection, or an ischemic insult to the peripheral or CNS but may also occur through a variety of other mechanisms. Injured nerve fibers develop ectopic activity and fire spontaneously or at a lower threshold *(1–5,18,19)*. The key concepts of chronic neuropathic pain involve both the inappropriate excitatory activity of nocioceptors and the resulting changes in the central processing of sensory input that amplifies and distorts the signal.

Hyperalgesia

Following an acute injury a normal enhanced response to pain, primary hyperalgesia, develops. In response to the depolarization produced by a painful stimuli, the primary afferent nocioceptors release excitatory neuropeptides, such as calcitonin gene-related peptide (CGRP) and substance P, that sensitize the primary afferents at the site of injury and produce vasodilatation and plasma extravasation in a process termed neurogenic inflammation *(1,3–5,20,21)*. Neuroinflammatory mediators released from inflamed or traumatized tissue, such as prostaglandins, bradykinin, leukotrienes, serotonin, histamine, cytokines, and free radicals from mast cells, macrophages, immune cells, and injured cells, further contribute to this peripheral nocioceptor sensitization *(1,21,22)*.

Another normal response seen after an injury is increased pain to mechanical stimulation in the surrounding uninjured skin called secondary hyperalgesia. This is also due to an enhanced responsiveness of nocioceptors, however, it is not a peripherally mediated phenomenon but rather is the result of recruitment of otherwise silent nocioceptors by the central release of excitatory neuropeptides *(1,6,22)*. Both primary and secondary hyperalgesia are an important evolutionary adaptation to injury, and disease as a heightened local response to pain promotes injury recognition, rest, and immobilization, promoting healing and reducing the risk of re-injury.

Pelvic Neuroanatomy

The female pelvis consists of somatic and visceral structures and accompanying sensory, motor, and autonomic nerves. The somatic structures include the following: muscles and skin of the abdominal wall and pelvic floor and the accompanying fascia, and the bony structures—the ischium, ilium, and sacrum. The visceral structures include the following: uterus, adnexa, vagina, bladder, urethra, ureters, and large and small bowel.

Somatic Nervous System

The somatic efferent motor neurons originate in the anterior horn of the spinal cord; innervation to the sphincters and pelvic floor muscles specifically arises from Onuf's nucleus, a densely packed group of atypical alpha motor neurons at S2–4 *(23,24)*. The afferent sensory fibers that transmit nocioceptive stimuli originate in the dorsal root

ganglion and travel distally to the somatic structures and proximally in the dorsal nerve roots to the dorsal horn of the spinal cord; however, some sensory afferents actually enter the spinal cord through the ventral roots *(24,25)*.

The skin and muscles of the abdominal and parietal peritoneum receive sensory and motor innervation via spinal levels T6–L2 *(25,26)*. The muscles of the pelvic floor and the skin of the vulva are innervated by spinal segments L4 through S4 from the sacral plexus although the mons and labia also receive sensory innervation from L1L2 through the ilioinguinal and genitofemoral nerves *(25,26)*.

There are eight named nerves and several direct branches that originate in the sacral plexus including the pudendal nerve *(23,24)*. The pudendal nerve has three main branches: the dorsal nerve of the clitoris providing sensory innervation to the clitoris, the inferior rectal nerve with sensory and motor innervation to the anus, and the perineal nerve with sensory supply to the labia, distal urethra, detrusor/bladder, lower vagina, and sensory and motor supply to the muscles of the pelvic floor and external urethral sphincter *(23,24,26,27)*. The levator ani muscles are innervated by both the pudendal nerve and direct branches from S3 to S5 *(23,24,28,29)*.

Autonomic Nervous System

The pelvis has a diffuse network of autonomic nerves that converge in the superior and inferior hypogastric plexuses. These neurons innervate the viscera and vasculature of the pelvis providing nocioception, integration of responses from the endocrine system, and regulation of smooth muscle functions such as vasoconstriction, visceral distension and contraction, and gastrointestinal motility. The autonomic nerves are intimately involved in sequencing for the complex coordinated events required for urine and fecal storage, micturition and defecation, parturition, and sexual responses.

Sympathetic Nervous System. The sympathetic efferents originate as preganglionic neurons in intermediolateral cell column of the spinal cord from T1 to L2 and then exit the spinal cord through the anterior root *(7,10,24)*. The sympathetics innervate muscle and skin through the spinal nerves or travel to the paravertebral ganglia or sympathetic trunk before descending in the retroperitoneum to form a complex series of plexuses with multiple interconnections prior to innervating the viscera and blood vessels *(7, 8,10,24,30)*. The sympathetic afferents receive sensory input from the muscles, skin, vagina, cervix, uterus, base of the bladder, the proximal urethra, and anorectum and ascend to the spinal cord through the complex series of retroperitoneal sympathetic plexuses to the cell body in the dorsal root ganglia; innervation from the abdomen and pelvis is received at spinal levels T6–L2 *(7,8,10,24,30)*.

Uterine and bladder nocioception is mediated through the sympathetic nervous system with little contribution from somatic neurons *(10,13,31–33)*. The sympathetic fibers also convey remarkably detailed information to the CNS regarding reproductive status and the menstrual cycle *(10,13,31–33)*.

The Parasympathetic Nervous System. The parasympathetic innervation to the ovaries, small bowel, and colon proximal to the splenic flexure originates in the brainstem and descends to the pelvis through the vagal nerve; the parasympathetic innervation to the distal colon, pelvic viscera, and erectile tissue of the clitoris originates in the interomediolateral cell column of the spinal cord primarily at S3 or S4 *(7,8,10, 11,23,24)*. The parasympathetic fibers exit the sacral spinal cord through the anterior root, merging to form the splanchnic nerves *(7,8,24,30)*. The vagal and splanchnic nerves intermingle with the sympathetic nerves in the hypogastric plexus and then

travel to their respective end organ where they synapse with post-ganglionic neurons *(8)*. The parasympathetic plexuses are smaller than their sympathetic counterparts and located at or in the smooth muscle of the targeted end organ *(8,23,24)*. The parasympathetic afferent fibers appear to have an inhibitory role in somatic and visceral pain perception *(8,34)*.

Enteric Nervous System. The gastrointestinal tract has an additional nervous system that regulates the function of smooth muscle, mucosa, and vasculature to coordinate intestinal behaviors such as peristalsis, secretion, and blood flow. The enteric nervous system (ENS) is a large neural network contained within the walls of the digestive tract and is a distinct system that integrates neural input and coordinates the complex sequencing required with gastrointestinal functions *(35,36)*. The ENS contains sensory neurons, excitatory and inhibitory motor neurons, and interneurons; peripheral placement of this neural network at the end organ decreases the burden on the CNS *(35)*. Unlike the autonomic nervous system where the ganglia function as relay stations for signals traveling to and from the CNS neurons in the ganglia of the ENS form a self-regulating network that process information and effect changes in the gastrointestinal tract through efferent signaling; this has been described as a minibrain within the walls of the digestive tract *(35,36)*. The CNS is involved in receiving sensory input from the gastrointestinal tract through interconnections between the ENS and the autonomic nervous system and the CNS can exert control over gastrointestinal functioning through efferent activity to interneurons.

Pelvic Nocioception and Convergence

The peripheral specificity from the pelvis is lost when it arrives in the CNS in a process involving cross-system viscero–viscero–somatic interactions *(7,11,12,20,31, 37,38)*. Pelvic structures share the same segmental innervation from S1–5; neurons from the peripheral nervous system (PNS) converge centrally in the sacral spinal cord with input from viscera, skin, muscles, and blood vessels. A large number of spinal neurons are receptive to visceral afferents, but there are no second-order spinal neurons that specifically transmit visceral signals so there is convergence of both somatic and visceral input onto the same second-order neurons *(7,9–11)*. The information that is received in the CNS (dorsal column nuclei) is re-distributed to many CNS regions with multiple interconnections.

These cross-system interactions or convergence between somatic and visceral structures are integral to the coordination of the multiple and often simultaneous actions of the pelvic floor, urinary, gastrointestinal, and reproductive tracts *(8,10,12,23)*. This framework allows for coordination of actions and responses not only to meet bodily functions but also to respond appropriately to physiologic changes, reproductive status, stress, infection, and injury. Clinically this shared segmental innervation explains vaginal hyperalgesia, urinary urgency, frequency, and acute pain in response to bladder inflammation from a urinary tract infection and reflexive abdominal guarding to peritoneal inflammation.

CHRONIC PELVIC PAIN

Chronic pain is defined by the IASP as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” Chronic pain results when excitatory synaptic transmissions persist, are

amplified or distorted, when normal modulating responses are suppressed, or when abnormal pathways develop. An essential concept is that chronic pain is a disease process unto itself. There are many factors involved in the transition from acute or episodic pain to chronic pain. While there may be triggering pathology, such as surgical trauma or endometriosis, one of the primary mechanism involves changes to the CNS. The ability of the nervous system to adapt to injury or pathophysiologic changes is an essential function, termed neuroplasticity, however, maladaptive responses of the neural network result in chronic pain.

Peripheral Sensitization

In response to disease, injury, or inflammation, peripheral afferent neurons become sensitized by neuropeptides and inflammatory mediators resulting in increased cellular excitability with spontaneous neuronal activity and lowered thresholds to pain *(1,3,4, 18–22)*. In addition otherwise silent nocioceptors, unmyelinated primary afferents that do not normally respond to stimuli, may also be sensitized. Membrane remodeling, gene induction, and activation of microglia also contribute to this increased cellular excitability *(1,4,18,19,21)*. Abnormal sprouting from peripheral neurons in response to injury also results in spontaneous discharges and increased sensitivity to excitatory neurotransmitters. Clinically, this peripheral sensitization presents as hyperalgesia and allodynia and is the hallmark of neuropathic pain. Diseases such as endometriosis and interstitial cystitis may produce peripheral sensitization contributing to persistence of pain after eradication of local disease or exterpritive procedures.

Wind-Up Response

The term wind-up applies to the phenomenon of reversible synaptic plasticity from painful stimuli *(18,21,39)*. Repeated low-level or noxious stimuli to C-fibers results in summation of these potentials (wind-up) producing a cumulative depolarization that results in increased glutamate sensitivity *(6,18,21,39)*. Clinically this translates to the same noxious stimulus producing more and more pain with each successive exposure *(5,6,39)*. Wind-up appears to be primarily mediated through the *N*-methyl-D-aspartate (NMDA) receptor complex and although it is believed to be a normal consequence of acute pain it is also believed to be the first phase of central sensitization although it is unknown why the process is reversible for some while others progress to central changes that lead to chronic pain *(6,18,21,22)*.

Central Sensitization

Central sensitization represents an enhanced response to nocioceptive inputs by the CNS and is the major mechanism of pathologic or chronic pain. It is characterized by hypersensitivity of dorsal horn neurons to both noxious and non-noxious stimuli producing sustained excitatory post-synaptic responses and reduced inhibitory control. This central response persists long after the nocioceptive input has ceased. It may also occur spontaneously, without any triggering pathology.

Upregulation of the NMDA receptor and enhanced glutamate sensitivity are known to play one of the key roles in the development of central sensitization. There are also many other contributing mechanisms such as increased presynaptic release of neuroinflammatory transmitters, increased post-synaptic response to neurotransmitters,

alterations in second messengers, and protein kinase activation *(6,18,21,22,39)*. There are also changes in gene expression and transcription contributing to chronic pain *(1,6)*.

Another key event in the dorsal horn involves the wide dynamic range neurons in lamina V. These neurons receive input from both low-threshold mechanoreceptors and primary nocioceptive neurons and do not normally respond to non-noxious or subthreshold stimuli. Once excited, however the second-order neurons of lamina V discharge at a high rate producing allodynia, the perception of non-noxious stimuli as pain *(6,18,21,22,39)*.

Sympathetic Activation

For some patients, chronic pain may be sympathetically maintained. Nociceptors may develop a sensitivity to noradrenaline, may be upregulated by increased catecholamine release, and activation of central alpha receptors may also occur *(1)*. Other contributors to sympathetically maintained pain include abnormal sprouting of sympathetic fibers in areas of injury of disease and incorporation of sympathetic fibers in neuromas *(19)*. The most minor injury can result in sympathetically mediated pain, as is seen with reflex sympathetic dystrophy.

The role of the sympathetic nervous system in chronic pelvic pain is significant given the rich sympathetic innervation of the pelvic viscera and the stimulation of alpha adrenergic receptors in response to visceral stimuli and inflammation *(7,12)*. In addition the cross-system inflammatory changes in the uterus characteristic of viscero–viscero–somatic convergence can be prevented with hypogastric neurectomy and endometriosis implants in animal models develop independent sympathetic innervation *(31,37,40,41)*.

Loss of Inhibitory Control

After pain is perceived in the brain descending inhibitory pathways are activated in the periaqueductal gray matter and dorsolateral fasciculus (Lissauer tract) of the spinal cord. Transmission of the nocioceptive stimuli is modulated by a variety of mechanisms including endogenous opioids, release of neurotransmitters serotonin and norepinephrine, and release of the inhibitory neurotransmitter GABA (gama-aminobutyric acid) *(42,43)*. Descending modulation increases in response to injury and inflammation and is intertwined with the cognitive, attentional, and motivational aspects of pain *(1,42,43)*. These mechanisms counteract hyperalgesia and allodynia; the more dorsal horn activation the greater the input from the descending inhibitory neural network.

The intensity of pain is modulated by these descending pathways initially pain intensity is suppressed to allow "flight or fight" response to injury subsequently there is a reduction in inhibitory control and an increase in pain to limit movement of injured tissues to aid recovery. An imbalance in descending inhibitory control may be a key point in patients with pelvic pain especially considering input from viscera and deep structures produce more dorsal horn excitability when compared with cutaneous tissues *(17,42,43)*. Changes in activation of the insular and frontal cortical regions on functional magnetic resonance imaging (MRI) in women with chronic vulvar pain support a central augmentation of sensory processing *(44)*.

Some patients with chronic pain are somatically hyperaware with multiple symptoms across several organ systems or intolerable side effects from low doses of mediations. For some this may truly represent somatization; however, for others this may reflect an

end disturbance of the CNS with loss of descending inhibitory control and an inability of the CNS to correctly interpret a variety of somatic and visceral inputs *(45,46)*.

Convergence

There are no distinct second-order neurons for viscera, therefore visceral and somatic afferents converge on the same second-order neurons in the CNS; viscero–somatic convergence is a required function for the complex sequencing of the urinary, gastrointestinal, and reproductive tracts. While these intimate connections are required for normal physiologic functions, they also allow a visceral or somatic pain condition to enhance or facilitate pain in other structures sharing the same segmental innervation *(10,20,37,38,41,47)*. For example, rats with surgically induced endometriosis exhibit more pain behaviors than controls in response to ureteral ligation and women with dysmenorrhea experience more referred muscle hyperalgesia from ureteral calculi as compared with women with no history of dysmenorrhea *(31,37,48–51)*. Interrupting the neural connections in the animal models or adequately treating dysmenorrhea prevents this exaggerated response to pain, therefore these enhanced responses to painful stimuli must be the result of increased release of neuroexcitatory transmitters and sensitization in the shared spinal segments *(48–52)*.

The neuroinflammatory changes can spread segmentally in the dorsal horn producing both referred pain and referred pathology *(7,15–17,20,31,37,47,50,51,53)*. This phenomenon explains how animals with endometriosis have reduced bladder capacity and chemically induced inflammation of the uterus or colon produces inflammation in distal sites such as the skin and the bladder *(51,53)*. In animal models interstitial cystitis can be induced by a neurotrophic virus that produces a neuroinflammatory response; the spread of both the pain and pathology can be prevented by interrupting the neural connections *(54)*. Convergence allows neurogenic inflammation and consequently both pain and pathology to spred between organ systems contributing to the complex nature of chronic pelvic pain *(45,52)*.

Central Nervous System Vulnerability

There is an increased incidence of non-pelvic and systemic pain syndromes, such as migraines and fibromyalgia among women with chronic pelvic pain *(55,56)*. In addition many women with chronic pelvic pain exhibit a heightened response to painful stimuli in sites distant from the pelvis *(57–59)*. These findings suggest some form of systemic nervous system involvement beyond central sensitization such as a biologic vulnerability to pain.

Depression, like pain, is also related to an imbalance of excitatory neurotransmitters and is not only increased among women with chronic pelvic pain but is a negative prognostic factor *(60,61)*. Depression is associated with increases in brain-derived neurotrophic factor (BDNF), an excitatory neurotransmitter that also contributes to neurogenesis, and so depression may contribute to PNS and CNS changes that increase the vulnerability to chronic pain or be a marker for some other CNS mechanism that facilitates the development of a chronic pain syndrome *(60,61)*.

CONTRIBUTING MECHANISMS

Hormonal Contributors

In the USA 61% of chronic pain patients are women; this female predominance starts at menarche and decreases at menopause suggesting a hormonal component in the development and/or maintenance of chronic pain syndromes *(65–65)*. Gonadal hormones are known to affect sensory processing and both estrogen and progesterone receptors are present in the CNS. In rats estrogen lowers micturition thresholds; rats also exhibit more hyperalgesia in the proestrus phase when hormone levels are high as compared to metestrus and diestrus when hormones levels are lower *(66,67)*. The menstrual cycle is known to affect both bladder pain and urge to void in women with interstitial cystitis with the least effect in the follicular phase and highest pain scores premenstrually; cyclic pain is also characteristic of endometriosis *(68,69)*. The menstrual exacerbation of pain syndromes appears to be a systemic phenomenon as it is not only well described with pelvic pathology such as interstitial cystitis and endometriosis but also with distant pain syndromes such as migraines *(69–71)*.

The effect of estrogen, progesterone, and other reproductive hormones on chronic pain is multifaceted and there are a variety of mechanisms by which they modulate the neurobiologic response. Estrogens regulate sensory and autonomic nerve density in the rat which increase post-ovariectomy *(72)*. Increased sympathetics may contribute to vasoconstriction or promote a sympathetically maintained pain syndrome; increased proliferation of sensory nociceptors may increase the burden of pain or contribute to increased release of sensitizing neurotransmitters *(72)*. Estrogen regulates nocioception at the cellular level through a variety of mechanisms including enhancement of neuroinflammation, increases in nerve growth factor (NGF), and changes in gene transcrition (*(73,79)*). Some studies indicate that pain responses maybe attenuated when hormone levels are high with both estrogen and progesterone exhibiting analgesic properties while other studies suggest that the effect of progesterone on the analgesic activity of estrogen is dose dependent with no effect at high levels and an inhibitory (i.e., algesic) effect at lower levels *(80,81)*.

Endometriosis-derived stromal cells are potent inducers of aromatase, more so than endometrium and adipose tissue *(82,83)*. Local production of estrogen may affect endometriosis-associated pain by stimulating invasion and spread of implants, promoting local growth of somatic and/or autonomic nerves, or by changing the estrogen/progesterone ratio. Aromatase activity has also been identified in the dorsal horn of the spinal cord so estrogens are also rapidly produced centrally affecting membranes excitability and nocioception *(76,79)*.

There are increases in polypeptides and other hormones with menstruation that also affect the pain response. Prostaglandins, algesic substances that sensitize nociceptors, are released by the endometrium at menstruation and produce painful uterine contractions local ischemia that further excites the peripheral nervous system *(84,85)*. Prostaglandins may also have central effects as they modulate the excitability of the tonic parasympathetic preganglionic neurons that regulate pelvic viscera *(86)*. Relaxin, a peptide hormone that promotes uterine relaxation and facilitates uterine stromal remodeling, varies with the menstrual cycle and has been identified in excessively high levels in a cohort of pregnant women with chronic pain *(87,88)*. Uterine arterial flow also increases substantially with rising estrogen levels therefore there may be an

increased flow of neurotransmitters, hormones, and algesic substances to the to pelvic organs premenstrually *(89)*.

Dysmenorrhea may further affect pain thresholds. It is unknown whether this is due to convergence, an increased release or sensitivity to prostaglandins, or an underlying vulnerability of the nervous system to pain. The increased somatosensory burden presented to the nervous system with dysmenorrhea may also facilitate the development of other pain syndromes. Women with dysmenorrhea report lower pain thresholds to both pain challenges within the uterine viscerotome and non-pelvic challenges (e.g., legs and arms) as compared with women who have no dysmenorrhea *(48)*. Increase in pain at sites not sharing common innervation support a central factor such as central sensitization, an underlying nervous system vulnerability to pain, or increased release and/or sensitivity to prostaglandins, as dysmenorrhea is primarily a prostaglandin-mediated phenomenon *(90)*.

Inflammation and Immune Factors

Neuroinflammation is an important contributor to chronic pain because of the actions of a vast array of inflammatory mediators, such as arachidonic acid metabolites, bradykinin, tumor necrosis growth factor-α (TNF-α), nitric oxide and ATP *(91)*. These inflammatory neuropeptides produce peripheral nocioceptor sensization, central sensitization, referred pain and pathology. Patients who develop chronic pelvic pain may have either an enhanced or an under-regulated neuroinflammatory process, such as the over production of BDNF seen in patients with depression *(60,61)*.

Other immunologic mechanisms may also be involved. Reduced levels of anti-inflammatory cytokines are seen among patients with fibromyalgia and impaired immunity contributes to post-herpetic neuralgia *(92,93)*. A deficit in immune surveillance of the peritoneum has been proposed as one hypothesis for the presence of endometriosis in only 22% of women despite the almost universal occurrence of retrograde menstruation. In addition increased peritoneal cytokines and growth factors, and deficits in natural killer cells have been identified among women with endometriosis *(94,96)*. Women with endomtriosis also have a higher incidence of systemic autoimmune and atopic diseases such as allergies and asthma *(97)*. Local inflammatory disturbances are common among women with vulvodynia such as cutaneous hypersensitivity to *Candida albicans* in skin testing *(98,99)*.

Genetics

Recent advances in sequencing the human genome support the concept that many patients with chronic pain may have a genetically vulnerable nervous system. Sodium channel mutations contributing to a variety of chronic pain syndromes have been described in addition to polymorphisms in a number of genes coding for neuropeptides such as BDNF, TNF-alpha, and interleukin 1 *(100–102)*. Polymorphisms in genes that code the NMDA and alpha-2 adrenergic receptors have also been identified *(100)*. Inheritable pelvic pain syndromes have been described including an autosomal-dominant visceral hypersensitivity and a gene on chromosome 13 (PAND1) associated with an increased risk of a syndrome of thyroid disorders, migraine, and panic disorder among some patients with interstitial cystitis *(103,104)*.

CONCLUSION

Chronic pelvic pain is a complex disorder that results when pathology in the somatic and/or visceral structures produces excitatory changes in the peripheral and CNS; nervous system plasticity and the neuroinflammatory response are the key factors in the spread of pain and pathology between organ systems and the development of central sensitization which contributed to the perpetuation of the disorder. Given the neurobiology chronic pelvic pain is unlikely confined to one organ system or to one mechanism, therefore it is vital to look beyond a disease-based model. Chronic pelvic pain has a complex neurobiology involving peripheral pathology, local and central effects of neuroinflammatory peptides, nervous system sensitization, and convergence. These mechanisms are further affected by a complex hormonal environment, the inflammatory and immune response, and genetics. The multitude of these pathophysiologic mechanisms underscores not only the complexity of this disease process but also the uniqueness of the individual pain experience.

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2 Acute and Chronic Flank Pain

Mark J. Noble, MD

Summary

Flank pain has multiple etiologies including but not exclusive to the genitourinary system. Treatment begins with a thorough history and physical examination. Before executing surgical treatment, the urologist would do best to evaluate a complete patient history, associated findings, and laboratory and radiologic tests to determine the cause of flank pain. A structured approach is recommended for diagnosis and treatment.

Key Words: Flank pain; kidney stones; renal infarction; renal vein thrombosis; papillary necrosis; ureteropelvic junction obstruction; renal tumors; urinary tract.

Contents

INTRODUCTION

Patients presenting with flank pain in the emergency room or the physician's office can sometimes pose a diagnostic dilemma. As a urologist who often must try to decide how to best help a patient with this complaint, I have through experience found that it is often not easy to determine the etiology of a patient's pain in this anatomic region. Usually, the patient is referred to me by a primary care or other physician who believes that the patient may have a kidney problem causing his or her pain. I have learned in more than 25 years of practice that there can be both subtle and not-so-subtle nuances to a person's flank pain that provide clues relating to etiology of the pain. There is also

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the "cause and effect" knowledge that relates historic, physical, x-ray, and laboratory findings to the type of pain and whether or not the pain can be resolved with one or another treatment applied to the urinary tract. For example, the finding of a ureteral stone with partial obstruction of the corresponding kidney in the setting of acute flank pain is thought to explain the pain because the pain resolves when the stone either passes or is surgically removed ("cause and effect").

Yet, even this type of situation, taken for granted by most doctors, is not an absolute because I have seen patients with stones in their ureters and resultant hydronephrosis who have absolutely no pain at all. Likewise, neurosurgeons have told me there are patients with numbness and pain along the course of a nerve along with compression by a disk, and this gets better with surgical decompression and removal of the disk, yet there are also patients with precisely the same magnetic resonance imaging (MRI) findings of disk(s) compressing one or more nerves who have absolutely no symptoms. Why is this so and how can we explain these seemingly contradictory observations? Although I am not a neurosurgeon and thus would have difficulty explaining differing symptoms for patients with lumbar or cervical disk disease, I will attempt to explain, based again on my experience and that of others in the field, how and why some instances of flank pain may relate to the urinary tract and alternately, why flank pain sometimes is unlikely to be due to a urinary tract etiology.

Even if I believe a patient with flank pain does not have a urologic cause for the pain, I am always careful to explain to the patient that I do not doubt he or she is having pain. Most individuals really do not enjoy going to the doctor, so I assume that a person is in my office (or the emergency room) because there really is a problem with pain. How, for example, can one prove or disprove that someone is experiencing a headache? One just needs to take the person's word for this and likewise for flank pain or any other type of pain. But if there is not a good explanation based on my evaluation of the urinary tract, then it means that I do not have a medical or surgical treatment (within my specialty of urology) to offer that would likely resolve the pain, and it then becomes necessary for me to refer the patient to someone else. If I think the pain is musculo-skeletal, I will refer the patient to an appropriate physician who treats spine or back or other disorders in that realm. If I think the patient needs to see a specialist in pain management, then I steer the patient in that direction. In fact, a current practice standard makes it a rule rather than an exception to refer a patient to a pain management specialist if the patient has chronic pain (pain lasting three months or longer) regardless of etiology. This presupposes that one cannot solve the pain issue. Even if the pain relates to one or both kidneys, there are instances when pain may be chronic or pain may recur so frequently it is much the same thing. One example would be the patient with medically refractory, recurrent stone disease, who despite all measures continues to form and then pass new urinary tract calculi several times each and every week! While there exist surgical remedies for this (ileal ureter substitution or renal autotransplantation), such are major and often high-risk surgeries and are generally considered a last resort *(1,3)*.

Many years ago, surgeons would sometimes operate solely to relieve pain with something like the following justification. "The kidney (or testicle, or whatever organ one chooses) is hurting the patient, even though it looks OK on x-ray, and the patient wishes the kidney removed, he (or she) is in fact convinced the pain must be from the kidney, his referring doctor is also convinced, so I'll remove it." Often the patient would have initial relief (of course the incision would hurt, but that was to be expected) only

to find the pain returned after a few months. The explanation was then of phantom pain, analogous to the recurrent pain some feel months after limb amputation, thought to be due to re-growth of nerves that formerly supplied the removed organ *(4)*. Regardless of the explanation, surgery is of variable help in these situations, so one should be very wary of intervention when there is no objective finding. Loin pain hematuria syndrome (LPHS) is an example of pain thought to originate within one or both kidneys with the only objective finding being the presence of hematuria (all other kidney tests and x-rays are normal) *(5)*. Some recent studies indicate permanent pain relief in such patients to be 50–60% at best *(6)*. When an operation succeeds about as well as flipping a coin, one might question whether indeed the operation or in fact the placebo effect was the reason for "success." In another study, capsaicin (an extract of chili peppers effective for various types of pain) produced 65% success in resolving pain in LPHS, so again one should be cautious before embarking on major or risky surgery simply to treat pain (especially when there are few or no objective findings) *(7,8)*. Medicine may not be an "exact" science, but we should always strive to be scientific with regard to treatments and their outcomes. In the discussion to follow, I hope that the reader will find that I have done so.

URINARY TRACT SOURCES FOR FLANK PAIN

Innervation of the Kidney and Ureter

The kidney, like other visceral structures, is richly supplied with nerves (Fig. 1 and Color Plate 1, following p. 132). Lower thoracic and upper lumbar autonomic nerve fibers synapse in the sympathetic trunk and then supply fibers that regulate renal blood flow and may influence hormone release *(9)*. Certainly, supra-renal fibers influence epinephrine release during stress. Parasympathetic fibers derived from the vagus nerve supply visceral afferent and efferent fibers to the kidney through the least and lesser splanchnic nerves; these very likely modulate organ-related pain *(10,11)*. Additional parasympathetic fibers from sacral levels supply the ureter and bladder and again regulate pain sensation as well as bladder smooth muscle contractility and ureteral peristalsis. These parasympathetic fibers can be blocked with muscarinic-blocking agents. For example, oxybutynin chloride relaxes parasympathetic nerves to the bladder and probably the ureter thus reducing contractility. Unfortunately, there is no real evidence that such is of benefit for pain emanating from the ureter. Likewise, muscarinic-blocking agents do not help with pain thought to originate from the kidney. It seems that analgesics, both narcotic and non-narcotic, are in fact best for this. Alternatively, we know that central nervous system (CNS) stimulators can directly block nerves at higher levels (in their paths to the brain) without drugs. This is not currently useful in the management of acute pain but is helpful for chronic pain *(12,15)*. Figure 2 and Color Plate 2, following p. 132 depicts the usual pain distribution for disorders at several levels within the urinary tract. This distribution is frequently seen in patients who are passing a kidney stone; it commonly begins in the ipsilateral costo-vertebral angle, radiates along the flank, and then moves down toward the groin and testicle (or labium majorum in a female) as the stone progresses down the ureter to the bladder.

Acute flank pain constitutes roughly 6% of the total in a recent tabulation of reasons for emergency room visits to hospitals in South Carolina *(16)*. This group included patients with pain from urolithiasis as well as flank pain from other causes. Statistics

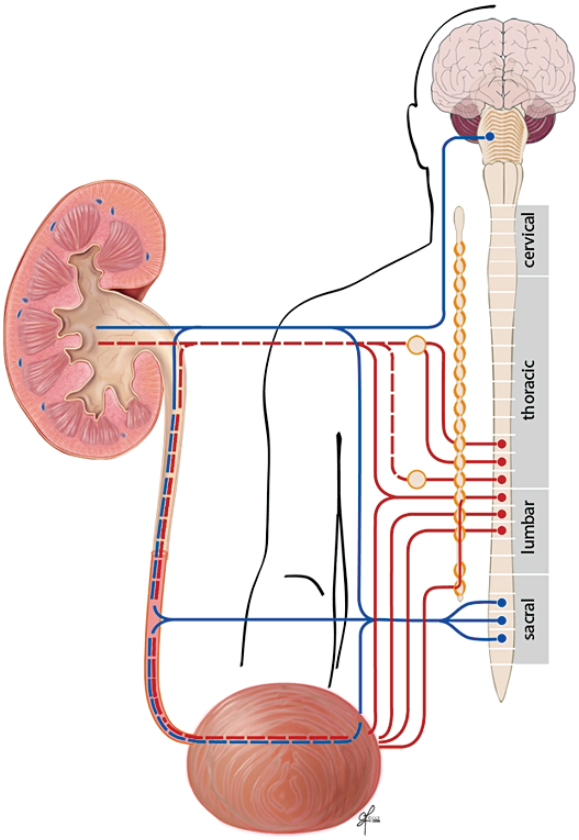

Fig. 1. Innervation of the urinary tract; blue for parasympathetic neural pathways and red for sympathetic fibers (*see* Color Plate 1, following p. 132).

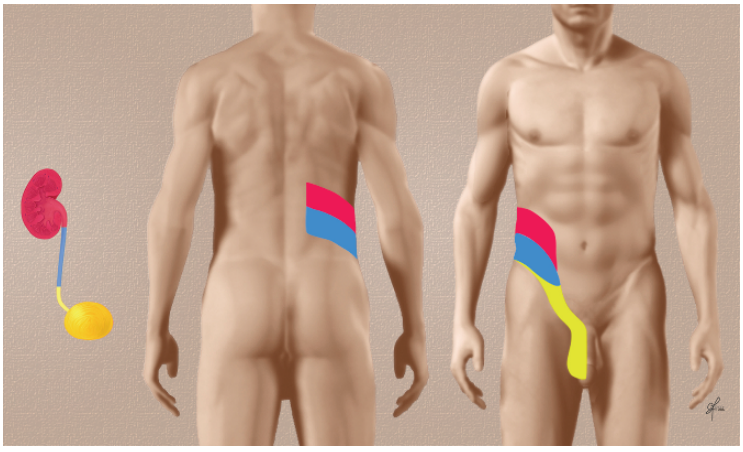

Fig. 2. Location of pain in the flank, right lower quadrant, and groin depends upon the location of pathology in the urinary tract, i.e., a stone making its way to the bladder. Red indicates pain originating in the kidney or at the uretero-pelvic junction (UPJ), blue shows pain from upper and middle ureteral pathology, and yellow indicates pain from the distal ureter or uretero-vesical junction (*see* Color Plate 2, following p. 132).

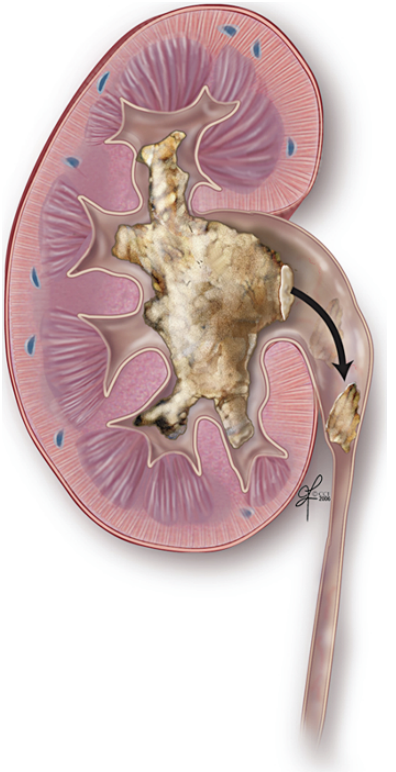

Fig. 3. A staghorn (branched) calculus sometimes can shed a stone fragment like a glacier calving an iceberg. This movement of stone within the kidney or from the kidney leading down the ureter can result in acute flank pain (*see* Color Plate 3, following p. 132).

from comparable sources demonstrate that approximately one ER visit in 15 in the USA involves acute flank pain that could indicate an upper urinary tract etiology or possibly some other extra-renal source that can mimic pain from the urinary tract. Because some causes of acute flank pain may be life-threatening, it is important to correctly diagnose the problem to avert a poor outcome for the patient.

Renal causes for acute flank pain include renal (Fig. 3 and Color Plate 3, following p. 132) or ureteral stone movement (Fig. 4 and Color Plate 4, following p. 132), intermittent uretero–pelvic junction obstruction (congenital or acquired), urinary tract infection involving the kidney such as pyelonephritis (Fig. 5 and Color Plate 5, following p. 132), acute renal carbuncle (Fig. 6 and Color Plate 6, following p. 132) or abscess, and events leading to focal or generalized renal infarction such as arterial embolization, renal vein thrombosis, and/or papillary necrosis (PN) (Fig. 7 and Color Plate 7, following p. 132) *(17,18)*. There are also some other, very rare causes for acute renal pain, such as hydatid cyst rupture into the renal collecting system, acute renal dysfunction due to uricosuria, and others equally obscure *(19,20)*. There may not be a perfect way to differentiate between some of these possibilities without the results of laboratory and radiologic testing, but judicious and careful use of clues contained in the history and physical examination should enable one to narrow down the choices fairly accurately to be efficient in ordering the appropriate, confirmatory tests.

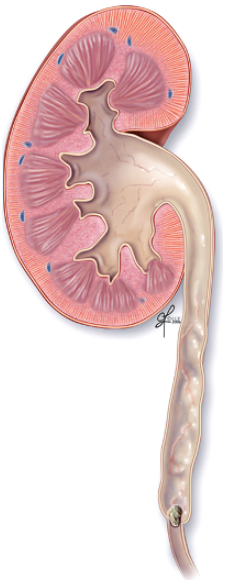

Fig. 4. A ureteral stone with resultant mucosal edema and hydro-uretero-nephrosis often presents as classic, acute flank pain (*see* Color Plate 4, following p. 132).

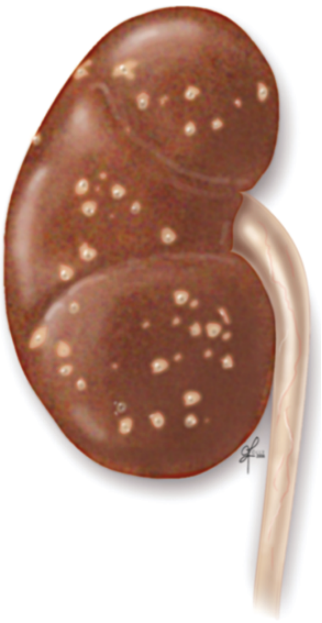

Fig. 5. This drawing depicts acute pyelonephritis with small cortical abscesses; patients with this presentation typically experience severe ipsilateral flank pain (*see* Color Plate 5, following p. 132).

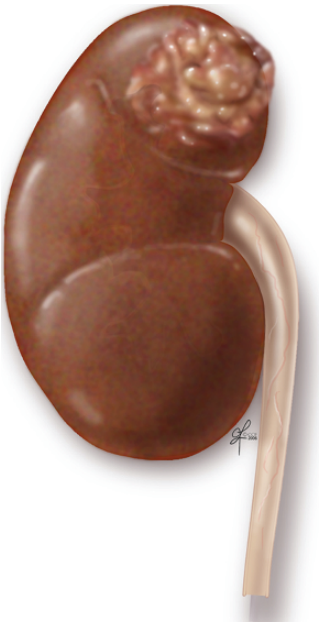

Fig. 6. Untreated pyelonephritis can sometimes lead to formation of a renal carbuncle, or abscess, depicted in this drawing. Patients with this pathology may have dull or sharp flank pain, usually with relapsing fevers and shaking chills. The pain can be acute, sub-acute, or chronic (*see* Color Plate 6, following p. 132).

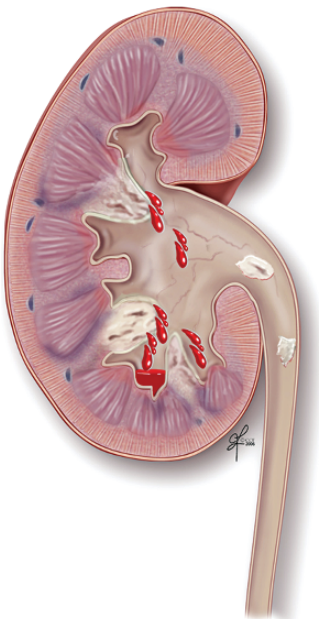

Fig. 7. Papillary necrosis is thought to represent an ischemic injury to the renal papilla. There are numerous causes including abuse of non-steroidal analgesics, diabetes, and sickle cell trait (*see* Color Plate 7, following p. 132).

Stones

One of the most painful conditions according to patients who have experienced many types of pain is that caused by a stone passing through the ureter. Roughly, 12% of adults in the USA have nephrolithiasis and approximately twice that percentage are found to have renal calculi if there is a positive family history for kidney stones *(21)*. This significant prevalence explains why kidney stone attacks are relatively common. It is unknown why a stone usually causes pain when it is moving in the ureter yet generally does not cause pain when not moving despite obstruction of the kidney (Figs. 8 and 9). Furthermore, a stone within the kidney is thought to rarely cause pain (Figs. 10 & 11 and Color Plates 8 & 9, following p. 132) unless it is moving so as to intermittently obstruct a renal segment or the uretero–pelvic junction (Fig. 12 and Color Plate 10, following p. 132) *(22)*. Some believe the explanation for stone-related pain is the sudden expansion of the renal collecting system compressing the renal parenchyma within a relatively non-elastic renal capsule. Others think the cause is obstruction-induced extravasation of urine which is sometimes seen when an intravenous pyelogram is performed. Now that non-contrast computerized tomography (CT) scanning is usually the x-ray ordered (due to greater sensitivity for detecting urolithiasis) *(23–25)*, urinary extravasation is not directly seen due to lack of radiographic contrast, but there is usually "peri-nephric stranding" outside the kidney which indicates an acute inflammatory response in the peri-renal fat; it is unknown whether this is due to extravasation of urine or some other inciting event *(26,27)*.

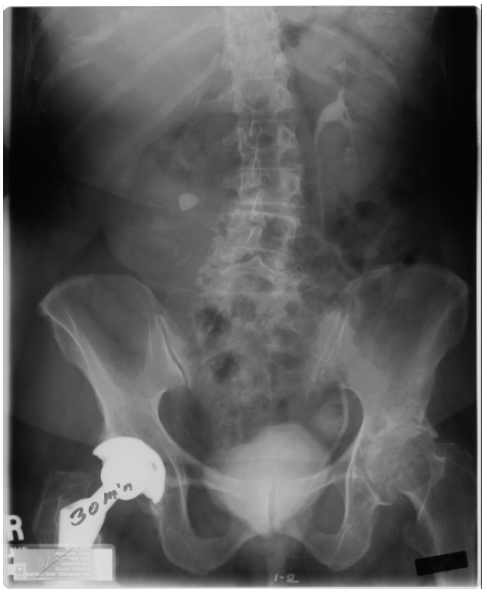

Fig. 8. This IVP (anterior view) shows normal excretion from the patient's left kidney and none from the right kidney. A triangular radiodensity is noted in the region of the right UPJ (uretero-pelvic junction) and is suspicious for an obstructing stone. Note the scoliosis concave towards the right kidney. Incidentally noted is a right hip prosthesis. Interestingly, this patient had no flank pain and denied experiencing any flank pain in the past.

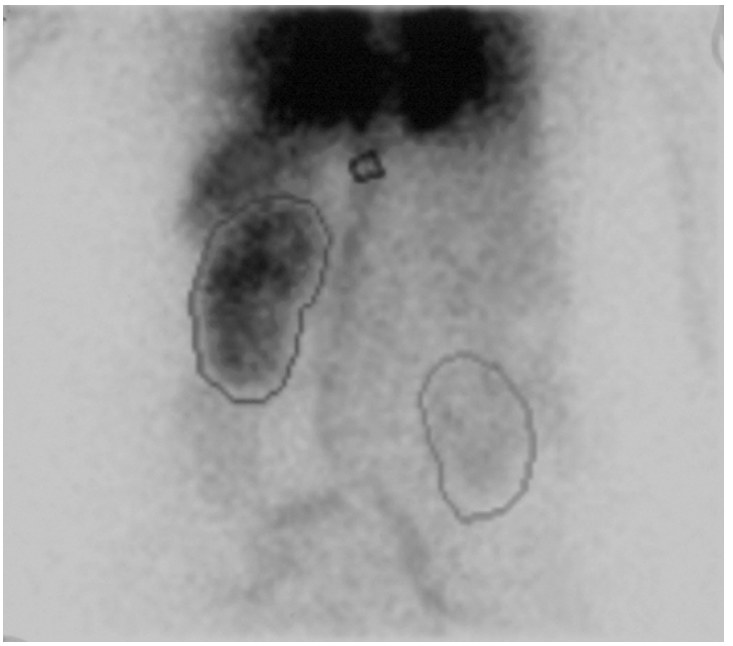

Fig. 9. This nuclear scan is from the patient who's IVP is shown in Fig. 8. It is a posterior view; hence the patient's right kidney is seen on the right side of the film. Note the right kidney is much lighter on this film (has far less radiographic uptake) than the left. In fact, measurements showed almost no function from the right kidney and in fact, the kidney had been obstructed for months or years.

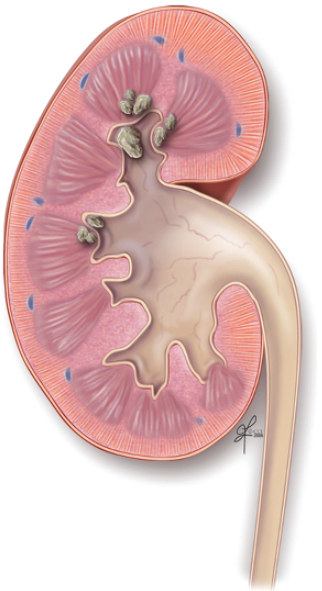

Fig. 10. This drawing illustrates a kidney with multiple, small, non-obstructing stones. Despite some disagreement from the urologic literature, most urologists including myself believe stones of this type rarely cause flank pain (*see* Color Plate 8, following p. 132).

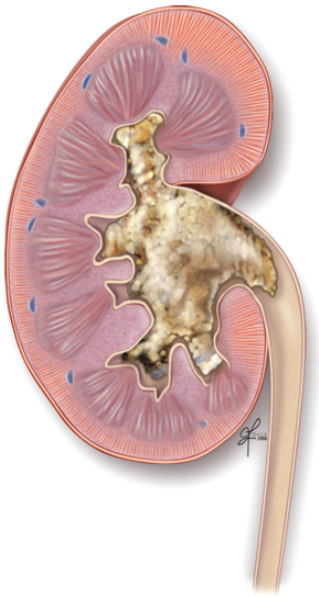

Fig. 11. This illustration shows a staghorn (branched) calculus with no loss of renal parenchyma (the kidney substance is not thinned out and there is no dilation of the renal collecting system around the stone). A stone this size requires months and usually years to form. The majority of patients I have treated with this finding do not have acute flank pain. If they did, the stone would be found before it became this large (*see* Color Plate 9, following p. 132).

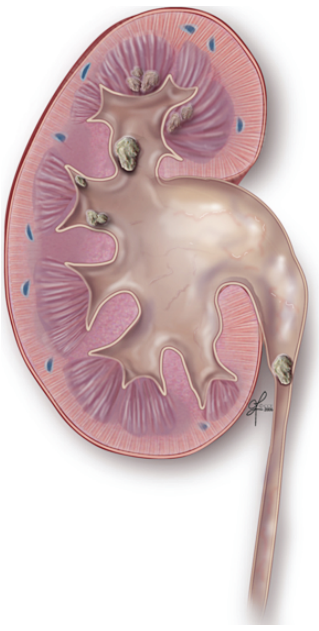

Fig. 12. A stone is depicting as lodging at the UPJ causing hydronephrosis. The patient might have congenital narrowing at the UPJ or the stone may simply be too large to migrate down the ureter. This usually presents as acute flank pain (*see* Color Plate 10, following p. 132).

Renal Infarction, Renal Vein Thrombosis, and Papillary Necrosis

Any event that causes death of a portion of an organ has the potential to cause visceral pain *(28–32)*. Renal infarction and PN both cause acute tissue death, while renal vein thrombosis may cause both acute as well as gradual tissue death *(33)*. One can simulate the pain of ischemia to an extent by inflating a blood pressure cuff above arterial perfusion pressure for a few minutes; the deprived extremity begins to feel quite a bit of discomfort within 5–10 min. If the tissue continues to be deficient in oxygen due to seriously impaired blood flow, irreversible cell death begins (in the kidney) in an estimated 30 min, and after 60–90 min (at normal body temperature), the kidney tissue will ordinarily be damaged beyond recovery (so far as renal function is concerned) *(34)*. This is quite a bit more rapid than ischemic damage to muscle tissue but of course takes place much more slowly than one observes for brain tissue, where 4 min is the limit at 37°C. In one study of renal vein thrombosis, only about 25% experienced "classic" symptoms of acute flank pain, proteinuria, renal swelling, sterile pyuria, hematuria, fever, and renal insufficiency; it may be that tissue damage or death is more gradual or swelling occurs more slowly so as to minimize patient discomfort *(29)*. Renal vein thrombosis is often helped with anticoagulation therapy and sometimes with thrombolytic therapy *(35)*, whereas neither renal infarction nor PN is helped with these modalities, hence, the importance of proper diagnosis. Acute renal infarction is usually accompanied by flank and/or abdominal pain, fever, hypertension (from ischemia-induced renin release), leukocytosis, micro-hematuria, and rise in serum Lactate Dehydogenase (LDH) *(36–39)*. Segmental or total renal infarction can also be performed as a therapeutic procedure by an interventional radiologist to help control acute, severe renal bleeding from cancer or trauma (or post-operative, delayed hemorrhage), and the resulting intense flank pain from this procedure is well known *(34,40)*. CT imaging with contrast can demonstrate lack of blood flow to a renal segment or to the entire organ and this is relatively quick. CT angiography is even more precise as is MRI *(28,36)*. Standard angiography may be required for more detailed diagnostic information depending upon the clinical circumstances *(34,41)*. Papillary necrosis may cause colic-like pain when there is sloughing of a renal papilla, and it passes down the ureter like a stone (Fig. 7). Etiologies include diabetic nephropathy *(42)*, sickle cell trait *(17)*, non-steroidal antiinflammatory agents (NSAIDS) *(43)*, and acute or chronic pyelonephritis. Sometimes, the causation is multi-factorial *(17)*. PN might not show on a CT scan except possibly as some hydronephrosis *(17,44)*, but PN should be suspected when a patient with diabetes, sickle cell trait, or other predisposing factor(s) presents with acute flank pain similar to that seen in a patient passing a stone yet no stone is found on x-ray studies and the appearance is not simply one of a "recently passed stone."

Ureteropelvic Junction Obstruction

Ureteropelvic junction obstruction (UPJ) may be congenital or acquired *(45,46)*. A typical history is one where the patient experiences flank pain after drinking large amount of fluids or after drinking alcohol or coffee (either of which may induce diuresis). Often the UPJ obstruction is intermittent; if it is constant, it may not produce acute pain symptomatology *(47,48)*. In cases where the UPJ obstruction is severe or high-grade, the renal parenchyma may be extremely thin and the kidney may have little or no residual function. In these instances, a nephrectomy rather than surgical

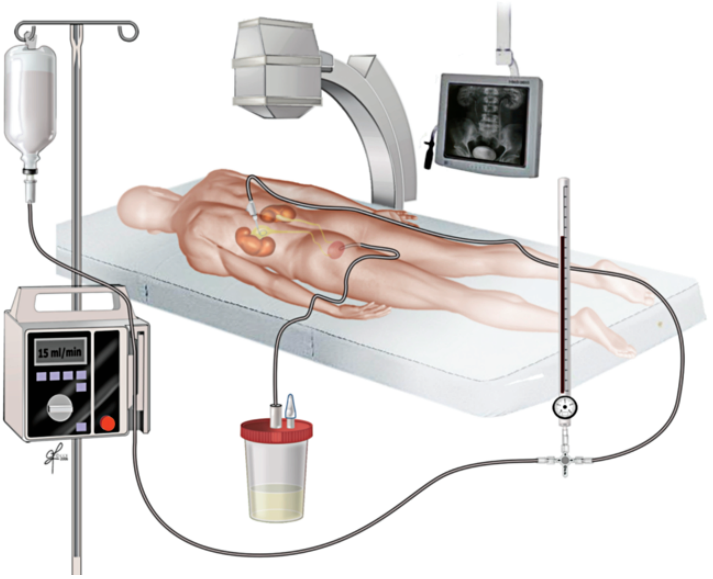

Fig. 13. The illustration shows a Whitaker Test with a manometer on a "T" connecter monitoring pressure while contrast solution is flowing into the patient's nephrostomy tube while fluoroscopy is being performed. This test is considered the "gold standard" for demonstrating UPJ obstruction and for duplicating flank pain thought to arise from such obstruction (*see* Color Plate 11, following p. 132).

repair may be the best course of action *(49)*. Figure 13 and Color Plate 11, following p. 132 depicts a study called the "Whitaker Test" which is a urodynamic study used to evaluate the upper urinary tract for the presence or absence of obstruction *(50)*. A small caliber percutaneous nephrostomy tube is inserted into the kidney and saline is infused while pressure is measured through a manometer. The bladder is drained with a catheter, and in some cases, bladder pressure is subtracted from renal infusion pressure. A Whitaker test is said to show obstruction if the intra-renal pressure rises above 15 cm of water at a saline flow rate of 15 ml/min into the nephrostomy tube. If pressure remains less than 10 cm of water at 15 ml/min flow rate, one concludes that there is no obstruction to drainage from the kidney. Pressures between 10 and 15 cm of water are in the "gray zone" or equivocal. This test is considered the most accurate way to evaluate a kidney for the presence or absence of UPJ obstruction; a nuclear renal scan (Fig. 14) or intravenous urogram with lasix washout is also helpful to evaluate UPJ obstruction, and although somewhat less accurate than the Whitaker test, lasix washout studies do not require a percutaneous nephrostomy tube and are therefore less invasive *(50)*. One helpful aspect of these studies would be the finding that the patient's flank pain is reproduced *during the study*. If the pain correlates with an abnormal study, then it is likely that surgical repair of the UPJ obstruction will be helpful in long-term resolution of the patient's flank pain.

Tumors

Renal tumors, both benign and malignant, are rarely thought to cause acute flank pain or other symptoms. Such is thought to be the reason that a high proportion of such lesions are either found incidentally by CT scan *(51)* or in fact are not found

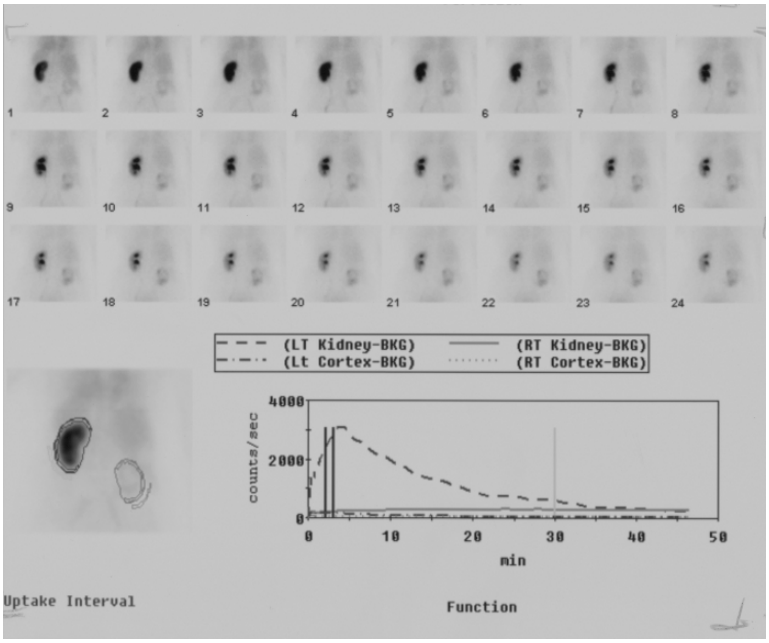

Fig. 14. This is a series of images from a MAG-3 renal scan with lasix washout. It shows severely diminished function of the right kidney due to UPJ obstruction. In this case, the obstruction resulted from the stone seen in figure 8, but a congenital UPJ obstruction that has caused severe loss of kidney function can appear the same.

until they have already become metastatic. The explanation is thought to lie in the comparatively slow changes that occur with gradual enlargement of a tumor within the renal capsular confines (compared to an acute infectious or stone event which incites renal changes over a short time interval). When pain does occur, it is often thought to be due to bleeding, either within the kidney or the retroperitoneum, that results from erosive growth of the neoplasm into a major artery *(18,52,53)*. Because pain from an acute stone event is far more frequent and the most sensitive test to detect stones in the urinary tract is the non-contrast (renal colic) CT scan, a renal mass causing the acute pain might not be readily appreciated, especially if it is not exophytic. One needs either a renal ultrasound or a CT with radiographic contrast to best detect renal neoplasms. The latter is not always safe or feasible due to increasing numbers of patients with intravenous contrast allergies, diabetes, renal insufficiency, or other conditions that constitute relative or absolute contraindications to a CT with IV contrast. For such patients, an alternative such as renal ultrasonography is usually available in the emergency room setting and this test should be considered when no stone is seen on the renal colic CT, when there is no perinephric stranding or inflammatory change (that might indicate a recently passed stone or an infection), and when there is microscopic or gross hematuria. More sensitive for evaluation of renal masses is MRI with contrast (rarely nephrotoxic* and not related to contrast used for conventional x-rays), but this type of study is not often available in an acute care

*Ergun, I., Keven, K., Uruc, I, et al.: The safety of gadolinium in patients with stage 3 and 4 renal failure. Nephrol Dial Transplant, **21**: 697, 2006

setting, especially at night or on holidays. In those instances where flank pain is due to acute bleeding from a renal or other retroperitoneal tumor, surgical resection has a high success rate in relieving the painful symptoms.

NON-URINARY TRACT SOURCES FOR FLANK PAIN

Sometimes flank pain is due to conditions unrelated to the urinary tract. As a urologist, I am often called to see patients with acute flank pain and a 1–2 mm calcification in the ipsilateral kidney found by means of a renal colic CT scan. There is no perinephric stranding, no hydronephrosis, and no other objective finding with respect to the urinary tract that might explain the patient's pain as arising from a renal or ureteral source. But once the patient is told there is a small stone in the kidney, the patient can become fixated on the idea that the pain must be from that stone despite widespread experience and reassurance to the contrary. It is important when evaluating patients with this type of presentation to remain sensitive to the patient's feelings and to take a thorough history in a non-confrontational manner. For example, a statement like "You have a very tiny stone in the kidney without obstruction, so your pain is not from this . . ." will often be counterproductive and upsetting to the patient. It may even result in a non-cooperative patient who thinks it's no use to speak with you any longer. It is far better to say, "I understand you are in a lot of pain and I will do all that I can to determine the cause and to help you but I need to ask you some questions to better understand your pain. . . ." Most patients will then be willing to discuss the pain in detail, how it started, what makes it better and what makes it worse, the character of the pain, if it has occurred in the past, and so forth. A history of recurring back and flank pain with bending or lifting is almost certainly musculoskeletal rather than from the urinary tract. A simple pulled muscle or ligament can produce extremely painful muscle spasms in the mid-or low back that can mimic acute flank pain arising from the urinary tract *(54)*. If the pain radiates down the thigh and perhaps into the leg, then nerve root irritation from a herniated disk is usually the etiology although Herpes Zoster and other disorders directly inflaming one or more nerves can produce similar pain, sometimes without rash or other clues *(55–58)*. Finally, a dissecting or rupturing renal artery or aortic aneurism with retroperitoneal bleeding may present with acute flank pain symptoms *(59,60)*. Usually, severe pain associated with an aneurism is sufficiently catastrophic that there are other signs and symptoms so the diagnosis is usually clear-cut, but on rare occasions (especially in the absence of severe bleeding), the presentation may mimic a urologic rather than a vascular source for the acute pain.

What are some of the ways that one may differentiate between urologic and non-urologic etiologies for acute (or chronic) flank pain? First and foremost, obtain a careful history regarding the pain as noted in the previous paragraph. Renal colic is not helped by remaining still nor is it aggravated by movement, whereas pain from a musculo-skeletal source is usually made worse with movement or position change. Likewise, pain from an intra-peritoneal source that radiates into the back, that is, acute cholecystitis, is usually made worse with movement, especially if the gallbladder is becoming gangrenous. Pain arising from the kidney does not normally move into the abdomen; it is virtually always flank or back in location (renal ectopy may be an exception but is fortunately quite rare). If the patient has right or left upper quadrant abdominal pain, suspect a source in the gastrointestinal tract rather than the urinary tract. Acute pancreatitis can present as acute flank and/or back pain (usually left side),

but there is almost always abdominal pain or tenderness as well *(61,62)*. One can often spot the patient with acute renal colic from across the room; the patient will writhe around or might even attempt to get up and walk "the walk" rather than lying still. It is quite characteristic. Other factors in the patient's history that increase the odds of a kidney stone etiology for an acute flank pain presentation include a previous history of kidney stones, a family history of kidney stones, or both *(21)*. On the other hand, if the patient gives a history of previous lumbar laminectomy for herniated disk, then the odds are increased that the pain is again related to a spine problem rather than the urinary tract. Inquire as to the presence of visible blood in the urine associated with the onset of the flank pain. Although gross hematuria is not always seen with ureteral colic, its presence increases the odds of a ureteral stone *(63,64)*. Nausea and/or vomiting is non-specific and its absence does not rule out a urinary tract stone problem, but the great majority of patients passing a ureteral stone will experience at least transient nausea and/or vomiting. Persistent nausea and vomiting is again more characteristic of a GI problem *(65)*.

Secondly, perform a careful examination to determine the precise location of the pain and whether it moves. Severe tenderness to palpation in the right upper quadrant over the location of the gallbladder is not suggestive of a kidney source for the pain. Pain over the sacro-iliac area in the lower or lower lateral back is most probably due to a musculoskeletal rather than a renal problem, whereas tenderness with palpation and percussion over the costo-vertebral angle more likely suggests a kidney source. A positive straight leg raising test is not typical for a renal or ureteral stone but again is more suggestive of herniated disk or sciatica although pyelonephritis with perinephric abscess formation could also result in worsening of the pain with straight leg raising *(66–71)*.

Thirdly, carefully review pertinent laboratory and radiologic studies. In one study, 92% of patients with ureteral calculi had gross or microscopic hematuria; in another it was 95% *(64,65)*. Although the absence of red blood cells in the urinalysis does not completely rule out a ureteral stone, its presence helps confirm the diagnosis (as well as other urinary tract etiologies such as PN, parenchymal injury due to sickle cell trait, and many other possibilities). Of course, a woman who is menstruating will have blood on urinalysis, so in such cases the presence of blood does not help with respect to the etiology of her flank pain. White cells in the urine (pyuria) with accompanying flank pain may indicate upper urinary tract infection, renal vein thrombosis, or some other condition that produces inflammation within the urinary tract. An elevated serum creatinine along with flank pain, especially if there is a hospital record of a normal creatinine level in the past, should strongly suggest some type of disease process involving the upper urinary tract(s). The finding of leukocytosis on a complete blood count is non-specific but significant (WBC $> 15,000$) and is uncommon with ureteral colic in the absence of urinary tract infection (uro-sepsis) *(65)*. Finally, a renal stone protocol CT scan that shows acute inflammatory changes, hydronephrosis, and/or one or more stones in the ureter helps point the way toward a urinary source for acute flank pain. If the CT scan does not show an acute process involving the kidney or ureter and there is no ureteral–pelvic junction obstruction, then a non-urologic etiology for the flank pain is most likely. On occasion, a renal colic CT scan will demonstrate a "possible small stone in the distal ureter without obstruction." If there is no gross or micro-hematuria or other significant laboratory finding, then one should be careful with regard to this type of CT finding, especially if the "possible stone" is 3 mm or smaller.

Both determining size of a radiodensity as well as differentiating a true ureteral stone from a phlebolith (that lies close to the ureter) are inaccurate with a non-contrast CT when there is no ureteral dilation *(72,73)*.

CONCLUSION

In this review, I summarized the disorders that frequently cause acute and sometimes chronic flank pain. I described characteristics of the pain as well as associated findings (laboratory, x-ray, and physical examination) that can help the clinician to differentiate between etiologies in a logical fashion. Finally, I presented my experience as a urologist who is often consulted to evaluate and treat patients with flank pain. One hopes that this may be of help to others trying to sort out what can sometimes be confusing and conflicting data while narrowing down the cause for the pain.

Throughout this discourse, it was assumed that the clinician attempting to determine causation for acute flank pain will have obtained a thorough history and will have performed a complete physical examination. These are important for formulating virtually any diagnosis and they provide the foundation for ordering the appropriate laboratory and radiologic tests needed to complete a patient's diagnostic work-up.

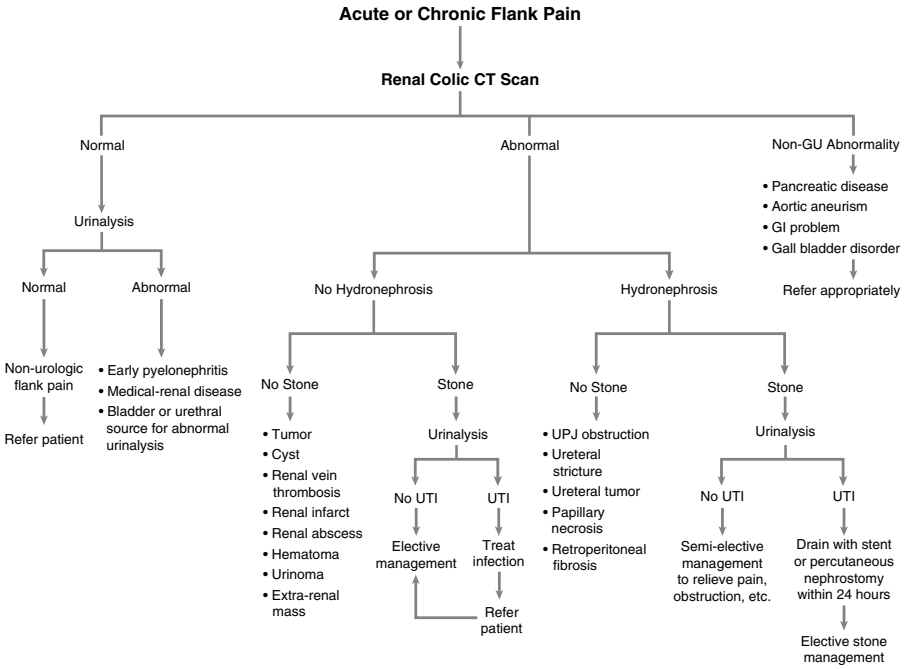

Fig. 15. My approach to sorting out acute and chronic flank pain is depicted in this flow chart. A renal colic CT scan and urinalysis are key to determining renal from non-renal sources for the pain after performing a thorough history and physical examination. Most non-infected stones can be managed on a semi-urgent bases with surgery indicated for intractable pain, severe obstruction, and/or failure of the stone to progress down the urinary tract. Infected, obstructing stones are a much more urgent problem due to the risk of septicemia and its complications. Many (but not all) causes for flank pain that are non-urologic can also be diagnosed by the CT scan; a diagnosis of musculoskeletal pain is sometimes one made by exclusion of acute urinary tract or other visceral causes for flank pain leaving "back pain" as the remaining explanation.

Indeed, the history and physical examination should point the way to the correct answer the majority of the time, with selected tests used to confirm the diagnosis. This is better than simple reliance on tests to provide the differential diagnosis without any thinking on the clinician's part.

Because there are many disorders resulting in flank pain and because it can be difficult deciding on a diagnostic approach for a specific patient, a structured approach may be helpful for the health care provider faced with this diagnostic challenge (Fig. 15). Hopefully, this will prove useful in the acute care as well as in the office setting.

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3 Pudendal Neuralgia

Pudendal Nerve Entrapment, Alcock Canal Syndrome, and Pudendal Canal Syndrome

Stanley J. Antolak, Jr., MD

SUMMARY

Pudendal neuralgia is a peripheral neuropathy of the pudendal nerve, generally due to compression between the sacrotuberous and sacrospinous ligaments. It is a tunnel syndrome. We have treated persons of both genders between 14 and 87 years of age. The characteristic symptoms are pelvic pains that are aggravated by sitting and driving and reduced by sitting on a toilet seat. Bowel, bladder, and sexual dysfunctions are common. The diagnosis is confirmed at physical examination of the pudendal sensory nerves. Objective neurophysiological tests include quantitative sensory testing of warm detection threshold and the pudendal nerve terminal motor latency test. Pudendal neuralgia is caused by repetitive flexion of the hip as in exercise and athletics, childbirth, sitting, and cycling. Treatment of pudendal neuralgia is analogous to treatment of the carpal tunnel syndrome. Nerve damage is prevented by a self-care protection program. When necessary, pudendal nerve perineural injection (PNPI) of local anesthesia and corticosteroids is necessary. Thirty percent or more patients require decompression surgery of the pudendal nerves. Each of these sequential treatments can provide prolonged relief of more than 5 years.

KEY WORDS: Pudendal neuralgia; pelvic pain; chronic prostatitis; perineal; suprapubic; inguinal; genital; vulvodynia; coccydynia; endometriosis; interstitial cystitis; obstructed defecation.

CONTENTS

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INTRODUCTION

In 1863, John Hilton of London, described a man with pain in whom it "was quite apparent that the cause must be associated with the perineal branch of the pudic nerve." He treated it by having "a hole made in his chair or to use a hollow cushion. Immediately, the symptoms began to subside and in three or four weeks they were all gone. Not a single thing was done but this. This patient was cured by removing pressure from the nerve and so giving it rest. This case does not stand alone" *(1)*.

Definition

Pudendal neuralgia is a neuropathy of the pudendal nerve that occurs in both genders. Pudendal neuralgia is characterized by perineal (and other pelvic) pain that is aggravated by sitting, generally decreased by standing and recumbence and typically reduced or relieved by sitting on a toilet seat *(2)*. The "pudendal territory" may include suprapubic, inguinal, genital, and perineal pain, vulvodynia, coccydynia, and proctalgia (proctitis fugax) *(3)*. Bladder, bowel, and sexual dysfunction occur *(4)*. Synonyms include pudendal nerve entrapment or the syndrome of the pudendal canal (Alcock canal) *(5,6)*. Clinicians rarely associate these symptoms with pudendal neuropathy. Conventional diagnoses include "prostatitis" or "prostadynia" in males or endometriosis or vulvodynia in females *(7,8)*.

Anatomy

The pudendal nerve is a mixed nerve containing somatic and autonomic afferent and efferent fibers. The nerve trunk develops from the sacral plexus anterior to the piriformis muscle. It is generally composed of fibers from anterior sacral rami S-2, -3, and -4 although more complex segregation of sacral roots occurs *(9,10)*. The nerve follows the posterior surface of the sacrospinous ligament, passes anterior to the sacrotuberous ligament, and enters the Alcock canal. Terminal branches are the dorsal nerve of the penis (clitoris), perineal nerve, and inferior anal nerve. Branches of the pudendal nerve may innervate the pubococcygeus muscle. Robert discusses a branch to the obturator internus muscle. Small sympathetic and parasympathetic fibers from the sacral plexus may account for the bladder, bowel, and sexual symptoms. The inferior anal nerve may be completely separate from the main pudendal nerve trunk. It may penetrate the sacrospinous ligament. In 50% of cadavers, the inferior anal nerve exits the main trunk prior to the Alcock canal *(11)*. This accounts for variable responses to nerve blocks into the pudendal canal. The main pudendal trunk is longer in Caucasians than in Asians. Surgical anatomy is discussed below.

PATHOPHYSIOLOGY AND ETIOLOGY OF SYMPTOMS

Pudendal neuropathy occurs bilaterally more often than unilaterally. Causes include compression, stretch, direct trauma, and radiation *(12)*. Pudendal neuralgia is a functional entrapment where pain occurs during a compression or stretch maneuver. The neuropathy worsens due to repetitive microtrauma resulting in persistent pain and dysfunctional complaints *(13)*. The pudendal nerve is compressed during sitting and cycling and is especially damaged during motocross *(14–16)*. Perineal pressure from an orthopedic fracture table causes pudendal neuropathy including impotence *(17–19)*. Stretch of the nerve by straining with constipation and childbirth causes pudendal neuropathy measurable in the anal and urethral sphincters *(20–24)*. Fitness exercises, machines, weight lifting with squats, lunges, and leg presses or karate with kick boxing and rollerblading are all etiologic factors. Youthful sports are a common denominator, possibly related to bony remodeling of the ischial spines *(25)*. Driving over rough roads or farm fields *(26)* causes vibration trauma. Falls onto the buttocks cause pudendal neuralgia *(27)*. Iatrogenic neuropathy includes trauma during vaginal surgery and suture entrapment during colpopexy using the sacrospinous ligament *(28–30)*. Radiation neuropathy following treatment of carcinoma of the prostate may relate to vascular impairment, inflammation within the nerve, or perineural desmoplastic reaction *(31)*. We found very serious pudendal neuralgia in four patients after urine leakage had complicated hysterectomy or radical retropubic prostatectomy. Central sensitization plays an important role in aggravation and maintenance of symptoms in many patients.

SYMPTOMS

Symptom history is paramount for diagnosis. Pain aggravated by sitting/driving/exercise, reduced by recumbence or standing and relieved by sitting on a toilet, is pathognomonic. Table 1 includes symptoms that respond to pudendal nerve blocks. Symptoms of interstitial cystitis occur in both genders.

The quality of neuropathic pain varies and may be described as burning, stabbing, ache, or pressure. Pain may occur anywhere in the pudendal territory. Primarily this includes the perineum, scrotum ("testicles"), and penis/urethra but extends to suprapubic, inguinal, crural, anal, coccygeal regions, and the upper medial thighs. Scrotalgia and vulvodynia occur with pudendal neuropathy *(32)*. Pain may be induced by voiding,

Table 1
Sites of Pain in Men with Pudendal Neuralgia: *N* = 88; ages 25–78; no prostate inflammation was found[a]

Unilateral scrotal/"testicular" pain	28%
Bilateral scrotal/"testicular" pain	12%
Penile/urethral	21%
Perianal	9%
Inguinal/suprapubic	5%
Ejaculatory	62%

[a] Represents the National Institutes of Health Category IIIB, non-inflammatory prostatitis, the chronic pelvic pain syndrome.

defecating, ejaculation, vaginal penetration, orgasm, or simply with an urge to void or defecate. Stress and changes in the menstrual cycle aggravate pain.

Urinary urgency, frequency, and slowing of the stream occur *(33,34)*. Erectile dysfunction, ejaculatory impairment, and painful ejaculation occur. Females may suffer reduced clitoral sensation, pain at vaginal penetration, reduced lubrication, and anorgasmia. Obstructed defecation, narrow stools, and changes in consistency occur *(35)*. Stress urinary incontinence, pelvic floor prolapse, and fecal incontinence are associated with pudendal neuropathy *(36,37)*.

Central sensitization (spinal cord wind-up) is apparent in some patients where aggravation of pelvic pain follows sexual arousal (e.g., reading a "steamy" novel). Foreign body sensation in the rectum, vagina, urethra, or perineum is frequent. This may be the golf ball that is common in men with prostatitis-like pains. However, dramatic objects may be a red-hot bowling ball, a pine cone, a fist, or even a stovepipe. The size of the object changes with intensity of the pain. The objects are eliminated with successful treatment of neuropathy. Sacral cord neuroplasticity causes pains in the calf and the dorsum, arch, and toes of the feet that are aggravated during pain flares and eliminated after treatment.

EVALUATION

Physical Examination

Physical examination focuses on a simple pudendal neurological evaluation. Pinprick sensation is tested at each branch bilaterally: dorsal nerve (clitoris and glans penis), perineal nerve (posterior labia and posterior scrotum), and inferior anal nerve (posterior perianal skin). Hyperalgesia is more common than hypoalgesia. Normal sensation to pinprick may occur even when quantitative sensory testing is abnormal. Pressure is placed on the nerve at the Alcock canal and medial to the ischial spine attempting to reproduce pain, bladder, or rectal symptoms—the Valleix phenomenon.

We evaluate the anal canal, sphincter, pelvic floor tone, and tenderness of the pelvic floor muscles. The parasacral area is examined for a back mouse (episacroiliac lipoma) *(38)*. We check for ilioinguinal and iliohypogastric neuropathies (vide infra). Concurrent involvement of these nerves will complicate the diagnosis, treatment, and control of symptoms. Inflammatory prostatitis must be excluded in male patients *(39,40)*.

Autonomic stimulation causes skin changes at the natal cleft, including cutis anserina and livedo reticularis, signs of the complex regional pain syndrome (Fig. 1). Neurogenic inflammation produces peau d'orange. Glanular cyanosis or labial erythema occurs. The scrotum may be tight with the appearance of a tennis ball. Unilateral labial contraction may occur.

Neurophysiologic

Several tests can measure pudendal neuropathy including sensory-evoked potentials, motor-evoked potentials, and motor latency tests *(41–43)*. Electromyography of the external urethral and anal sphincters and the bulbocavernosus and ischiocavernosus muscles may show denervation and reinnervation *(44–46)*. We prefer a quantitative sensory test called the warm detection threshold (WDT) *(47)*. WDT is a very sensitive test for pudendal neuropathy in our hands *(48,49)*. We use the NTE-2A Thermosensory Tester (Physitemp, Inc., Clifton, NJ) and follow a stepping algorithm *(50)*. Responses

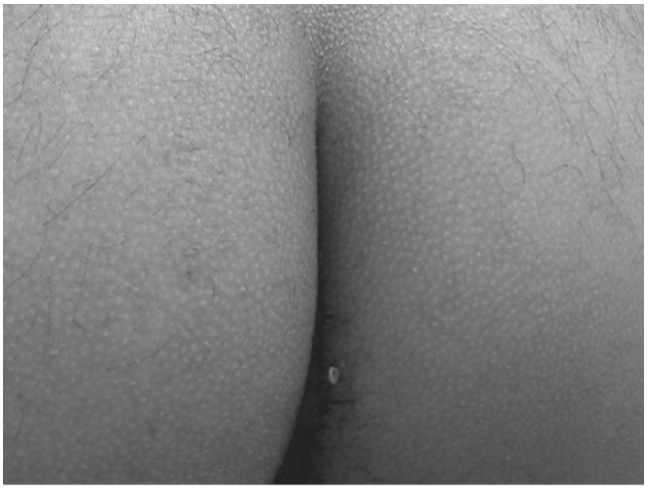


Fig. 1. Severe cutis anserina over the buttocks in a male with pudendal neuralgia.

Table 2
Warm Detection Threshold

Normal female			*Female with pudendal neuralgia*		
Site	*Left*	*Right*	*Site*	*Left*	*Right*
Clitoris	34.3	35.3	Clitoris	37.5	36.5[b]
Labium	34.8	35.0	Labium	37.5[a]	38.5[b]
Perianal	36.2	34.9	Perianal	41.5	> 43.5

Using the Physitemp NTE 2A Thermosensory Tester, following a stepping algorithm. Temperatures in C. Abnormal > 39°C.

Dysesthesia, metesthesia, and referred sensations in the pudendal distribution are neuropathic events suggesting spinal cord wind-up. They may be noted elsewhere in the sacral cord nerve distribution.

[a] Indicates cold sensation (dysesthesia) at normal temperature.

[b] Indicates hot sensation (dysesthesia) at normal temperature.

in one female are shown (Table 2). We perform the pudendal nerve terminal motor latency test using a St. Mark's surface electrode. It is specific but less sensitive.

Neuritic pains following electrical stimulus for neurophysiologic testing occur in 22% of males and 37% of females in our clinic suggesting spinal cord wind-up. Responses include dysesthesias at normal temperatures, metesthesia, pain referred to different ipsilateral or contralateral branches of the pudendal nerve or to the abdomen, suprapubic region, or feet. Bladder warmth or urge to void may also occur.

Imaging

Magnetic resonance imaging (MRI) of the lumbosacral spine and plexus evaluate the spinal cord and nerve roots. Abnormalities are rare, including one case each of metastatic tumor of unknown origin in the sacral canal, a pelvic floor hernia, and local recurrence of carcinoma of the rectum anterior to the sacrum. Tarlov cysts, identified

in nine patients, were deemed not to be the basis of patients' complaints because treatment with pudendal block relieved their symptoms. Judet views of the hips provide excellent images of the ischial spines. Magnetic resonance neurography is used by some practitioners to assist diagnosis. This technique awaits further study *(51)*.

TREATMENT

We recommend a sequential treatment program beginning with self-care (nerve protection), progressing as necessary to pudendal nerve perineural injections (PNPIs) and surgical decompression (Table 3). Historically, Bensignor recommended conservative treatment of pudendal neuropathy with a series of PNPIs using bupivacaine and corticosteroids *(2,52)*. Robert and Shafik developed early surgical techniques for decompression *(53)*.

Self-Care

Self-care is a program of nerve protection based on Robert's observation that sitting on a toilet seat relieves pains of pudendal neuralgia. Patients avoid sitting. When sitting is necessary, they use a "perineal suspension pad" fashioned quite inexpensively from a gardener's kneeling pad by cutting out the center (Fig. 2). The ischial tuberosities support the patient. The perineum is suspended. The ischioanal fat body descends, reducing pressure of the nerve against the falciform process of the sacrotuberous ligament. Activities that cause and aggravate pudendal neuralgia are discontinued, such as cycling, hip flexion activities including leg presses, Stairmaster®, ab crunches, jogging, and rollerblading. Walking on a flat surface and doing pushups are permitted.

Table 3
Sequential Treatment of Pudendal Neuropathy

Self-care (nerve protection)	Avoid sitting. Use perineal suspension pad (mandatory). Discontinue cycling, bending, squats, weight lifting, and rowing. Cease hip flexion exercises including step aerobics, jogging, in-line skating, sit-ups, ab-crunches, stepping machines, piriformis stretches, and yoga. Cancel contract with fitness center. Amitriptyline is the initial medication offered. Symptom scores may normalize within 4 weeks. Self-care restrictions continue throughout treatment sequences
Pudendal nerve perineural injections (PNPIs) of bupivacaine and triamcinolone	Series of three blocks at 1-month intervals. Monitor symptom scores. A fourth block may be offered. Two PNPIs into interligamentary space between the sacrotuberous and sacrospinous ligaments. One PNPI into the pudendal (Alcock) canal. Blocks may be therapeutic or only diagnostic. Repeat series in 4–24 months depending on symptoms or proceed to decompression of the pudendal nerves
Decompression surgery	Transgluteal approach includes transection of the sacrospinous ligament with transposition of the nerve anterior and medial to the ischial spine. Symptom response occurs in 60–70% and may require 9–24 months. Improvement durable at 5 years. Normal activity is possible

Fig. 2. Perineal suspension pad. The center has been cut away from a gardener's sitting pad. Body weight is supported by the ischial tuberosities, relieving pressure on the perineum and decreasing pressure of the ischioanal fat body that compresses the pudendal nerve against the falciform process of the sacrotuberous ligament.

Climbing stairs backward, using a "pick-up" tool, and wearing slip-on shoes are helpful in cases of extreme pain. Mothers must avoid squatting to lift children.

We advice amitriptyline 10 mg at h.s., increasing every 5 days to a maximum of 50 mg, adjusting the dosage for side effects. Narcotics generally do not control neuropathic pain. Pregabalin is effective in only a few of our patients and often has bothersome side effects. Monitoring symptom scores demonstrates that pain and bladder function may improve dramatically using self-care. Cure for more than 5 years has followed self-care. Occasionally, patients return to jogging and cycling, using a hornless saddle (Fig. 3).

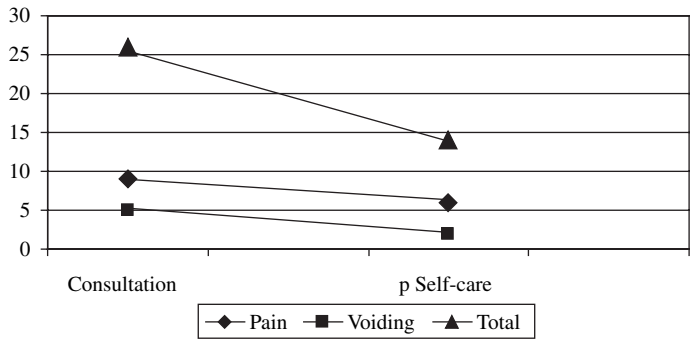


Fig. 3. Improvement in the National Institutes of Health Chronic Prostatitis Symptom Index after 6 weeks of self-care, $n = 17$ males. All changes are significant ($p = .001$) Pain and urination domains and total scores are illustrated.

Pudendal Nerve Perineal Injections

Historically, pudendal blocks relieve urethral sphincter spasms in paraplegics *(54,55)*. Pudendal obstetrical anesthesia was masterfully outlined by Klink *(56)*. Several authors describe the use of pudendal blocks to relieve chronic, non-malignant pelvic pain *(57–60)*. Symptom responses after PNPI help to define the protean neuropathic events of pudendal neuropathy.

Perineural anesthesia may be diagnostic or therapeutic. We recommend a series of three monthly, transgluteal injections of bupivacaine 0.25%, 6 ml, and triamcinolone 40 mg, 1 ml. Two PNPIs are given into the interligamentary space at ischial spine, and one is given into the Alcock canal. Those patients with side effects from steroids, or recent excessive steroids, receive 4000 units of heparin bilaterally *(61)*. Two hours after injection, examination of six sites with pinprick detects analgesia or hypalgesia [clitoris (glans), labia (posterior scrotum), or perianal area, bilaterally].

Accuracy of injections is imperfect, whether guided by palpation, fluoroscopy, EMG stimulation, or CT. Complete pudendal anesthesia correlates with a good therapeutic response. Patients monitor symptom indices weekly for 14 weeks.

Symptom relief after PNPI may last hours, days, or weeks. Symptoms may completely resolve after one, two, or three PNPIs. Bensignor described control of neuralgia in 70% of patients at 6 months after PNPI. Hough and colleagues performed more than 2300 PNPIs but did not summarize responses *(62)*. An early patient continues to have durable relief for more than 4 years including relief of serious pain, urinary retention, and erectile dysfunction *(63)*. Patients describe improved erections, decrease of pain following ejaculation, increased vaginal lubrication, pain-free intercourse, improved orgasms, improved defecation, and other subtle improvements. Lack of pain control following successful skin anesthesia indicates a higher lesion, that is, nerve root or spinal cord lesion (the double crush syndrome). Pain "flares" may occur, lasting several days before gradually declining to tolerable levels. We suspect microvascular neuropathy in a subset of patients, with previous pelvic surgery complicated by urine leakage, in whom PNPIs did not relieve their pains. Injections into the Alcock may not anesthetize the inferior anal nerve because that branch exits the main trunk proximal to the Alcock canal in 50% of cadavers.

Complications of PNPI are infrequent. Bleeding through the needle requires postponement of PNPI. Sciatic or posterior femoral cutaneous nerves may be affected causing transient gait disturbance. Penetration of the pudendal nerve by the needle apparently occurred in three of our patients causing significant aggravation of pudendal pain requiring up to 3 months for pain resolution. Incontinence of urine or flatus may occur for 1 or 2 h after PNPI.

Decompression Surgery with Transposition of the Pudendal Nerve

Approximately one-third of patients with pudendal neuropathy will require surgical decompression. Robert outlined the pathophysiology and the surgical anatomy of a transgluteal approach *(2)*. Perineal and transvaginal approaches are used *(27)*. Endoscopic and laparoscopic decompression of the nerve are described *(64)*. The transgluteal approach is advantageous because of the frequent surgical observation of anatomical variations that may be inaccessible through perineal/vaginal approach. These include a broad sacrospinous ligament and "tethering" of the nerve at the

supralateral margin of the ischial spine. The transgluteal approach also permits access distally into the Alcock canal.

An oblique incision is made between the sacral margin and the ischial tuberosity. Gluteal fascia is opened. Muscle bundles are separated to expose the sacrotuberous ligament. The ligament is opened axially to permit dissection anteriorly. An Omni Tract retractor (Minnesota Scientific, Inc., St. Paul, MN) improves access to the pudendal nerve and the sacrospinous ligament. The nerve is identified and elevated with a vessel loop. Dissection proceeds cranially, identifying and transecting any fascial structures compressing the nerve. The sacrospinous ligament is identified and transected. This releases tension from the nerve and permits transposition anteriorly and medially. Perineural varices often develop after relief of compression, a change typically identified at carpal tunnel surgery. The fibers of coccygeus muscle are separated from the ischial spine to permit transposition of the nerve medially and anteriorly to the ischial spine.

Proceeding distally, the Alcock canal is opened. Any adhesions or perineural fibrosis are released. An adhesion barrier is placed to minimize postoperative perineural scarring. A suction drain is brought through a separate stab wound. The sacrotuberous ligaments and gluteus fascia are approximated.

The patient stands on the evening of surgery and ambulates the following day. Typically, hospitalization requires 2 days. We advice a postoperative "gliding exercise." The hip is flexed and rotated laterally and medially, twice, bilaterally. Exercise is repeated twice daily for 1–2 years. Patients should not sit for 1 month except during meals. They continue to use the perineal suspension pad. Return to work varies from 10 days to 3 months. Some patients remain permanently disabled.

Pathologic Anatomy

Pudendal compression neuropathy has not been described in cadavers. Bony imaging and surgical observation provide the best anatomical information regarding pudendal neuropathy.

Judet views of the pelvis or fluoroscopy during nerve blocks usually demonstrate an elongated ischial spine with corresponding reduction in the area of the greater sciatic notch. Remodeling of the pelvis appears to follow youthful athleticism between 15, when the bone center appears, and 25 years, when ossification is complete *(25)*. The posterior and medial repositioning of the ischial spine places the sacrospinous and sacrotuberous ligaments in close proximity.

At surgery, the sacrotuberous ligament may be thick and indurated (Fig. 4). The nerve may be tethered to its anterior surface. The falciform process may be prominent. The sacrospinous ligament is quite variable. It may be a broad sheet over which the pudendal nerve stretches during flexion motions of the hip. It may have a sharp, firm superior edge that impinges the nerve. The sacrospinous ligament may be triangular with a firm ridge at its apex compressing the nerve against the anterior surface of the sacrotuberous ligament. Coalescence of fibers of the sacrotuberous and sacrospinous ligaments cranially may form an inverted funnel (Fig. 5). The aperture of this funnel may be extremely small, constricting the nerve. Tethering of the nerve at this site would cause stretching of the nerve during hip flexion. Randomly, along the nerve trunk, fibrous bands 1–10 mm wide may compress the nerve against the anterior surface of the sacrotuberous ligament. The bands prevent nerve movement causing stretch neuropathy. Occasionally, these bands penetrate the nerve. Coccygeus muscle bundles

Fig. 4. 64-year-old female. Surgical anatomy demonstrates the left inferior anal nerve (in upper vessel loop) penetrating the sacrospinous ligament. The sharp superior edge of the sacrospinous ligament is compressing the anterior surface of the pudendal nerve (in lower vessel loop) at the tip of the scissors. The posterior femoral cutaneous nerve, lateral to the pudendal nerve, is also compressed. The transected sacrotuberous ligament is elevated cranially.

may interdigitate with radiating bands of the sacrospinous ligament and "bind" the pudendal nerve. Distally, fibrosis within the Alcock canal may restrict the neural gliding mechanisms. Radiation fibrosis of the pudendal nerve has been identified with nerve compression. Discoloration of the nerve suggests devascularization. Intraoperative neurophysiologic testing proximal and distal to the compression can define neuropathy *(27)*. Perineural scar tissue has been identified fixing the nerve to the inferior pubic ramus and sacrospinous ligament. The inferior anal branch may be compressed as it penetrates through sacrospinous ligament. Inexplicable perineural fibrosis is occasionally present along the main nerve trunk or extending into the Alcock canal, affecting the three branches. Small diameter of the pudendal nerve following previous pelvic surgeries may reflect infarction or atrophy due to interruption of the vasonervorum.

Surgical Success

Case series report reduction of pain in 60–70% of operated patients *(2,27,65,66)*. Complete symptomatic cure occurs but is not common. Bladder, bowel, and sexual dysfunctions improve as illustrated in the male (Fig. 6). In a controlled study, durable improvement continued for 4 years in 9 of 12 cases. Unoperated controls were unimproved at 1 year *(67)*.

Surgical Complications

Approximately 5% of men and women require catheterization for retention after the indwelling catheter is removed. Wound complications in more than 200 nerve

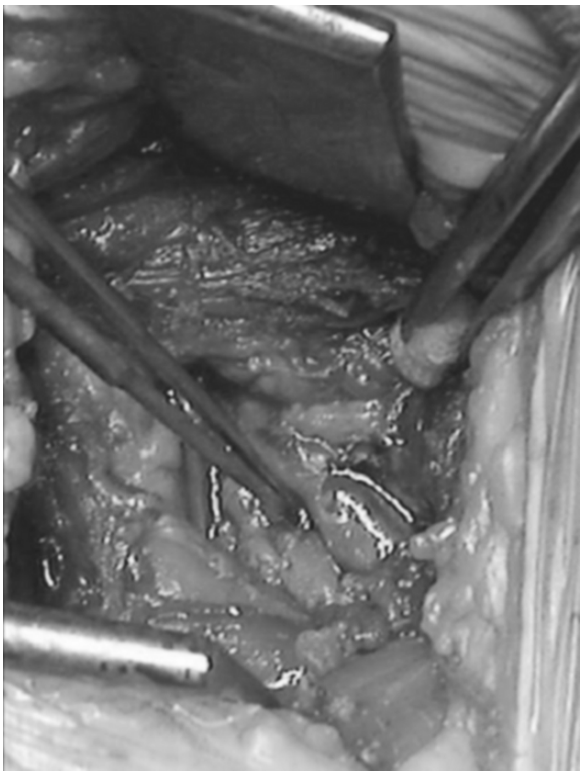
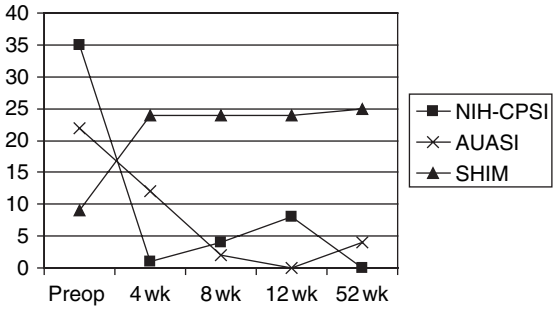


Fig. 5. 68-year-old male. A "funicular" interweaving of sacrotuberous and sacrospinous fibers has been opened (left of pickups) to expose the pudendal nerve and the posterior femoral cutaneous nerve (right of pickups). Both nerves have varicose veins that commonly appear after decompression of a nerve. Proximal to the pickups, both nerves (obscured) are compressed in the small, funnel-like aperture between the conjoined ligaments.



NIH–CPSI = National Institutes of Health Chronic Prostatitis Symptom Index
AUASI = American Urological Association Symptom Index
SHIM = Sexual Health Inventory in Males

Fig. 6. Postoperative symptom scores improve to normal. A 47-year-old male with 3 years of pain, sexual, bladder, and bowel dysfunction. Results are durable at 1 year.

decompressions are limited to one hematoma and one case of lobular, subcutaneous fat necrosis. One female developed pneumonia. Neuropraxia may occur and require several days to several weeks to resolve completely. One patient suffered reduced perianal sensation associated with incontinence of flatus but was normal 3 months after surgery. Pelvic instability is a potential problem if the sacrotuberous ligament is transected.

Failure of Surgical Intervention

Thirty to forty percent of patients fail to have significant relief following surgical intervention. Prolonged duration and severity of pre-operative symptoms are associated with poor results. Robert notes that failure of pain control also correlates with poor responses after pudendal nerve blocks. Unilateral surgery may require a later contralateral procedure to control symptoms *(68)*. Sympathetically maintained pain may be a factor. Pre-mature return to overenthusiastic exercise will hinder pain control.

Treatment of Postoperative Failures

Bensignor in Nantes, France, treated persistent pain by repeating pudendal nerve blocks of steroid and bupivacaine as soon as 2 months after surgery. He treated sympathetically maintained pain for 5 days using infusions of ketamine and clonazepam through epidural catheter. Hypogastric plexus blocks occasionally relieve persistent, sympathetically maintained pain.

We treat failures from several surgical venues using perineural blocks of bupivacaine and heparin 4000 units with 0.8 ml of $NaHCO_3$. Six weekly injections are given followed by gradual increase of the interval. The needle usually encounters dense scar tissue that requires significant pressure to infiltrate medications. With repeated injections, the perineural scar softens and infiltration of heparin solution meets less resistance. Pain, sexual, bowel, and bladder symptoms may resolve after one or two blocks. One patient returns every 3 months for bilateral blocks. He remains fully functional and no longer requires medications for Crohn's disease, suggesting control of parasympathetic stimuli. Conversely, a complete series may be unsuccessful.

Botox injections into the obturator internus muscle are used *(69)*. Other pain clinicians report anecdotal improvement using Botox, and this will require controlled study.

Popeney in Houston is beginning a study with bilateral sacral nerve root stimulation. A study of spinal cord stimulation is being performed at the Cleveland Clinic in patients with intractable chronic pelvic pain.

Reoperation has been performed by some surgeons identifying scar tissue or inadequate transection of ligaments (unpublished).

Monitoring Treatment of Pudendal Neuralgia

Multiple symptoms scores are available to the clinician or researcher. We use the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) in males and have developed a female modification (f-NIH-CPSI) *(70)*. This index has nine questions in four domains: pain, urination, impact of symptoms, and quality of life. We record the latter two together. The American Urological Association Symptom Index (AUASI) measures voiding symptoms that are common in patients with pudendal

neuropathy *(71)*. Sexual function is monitored using the short version of the International Index of Erectile Function called the Sexual Health Inventory in Males (SHIM) *(72)*. We use the Female Sexual Function Index (FSFI) although this questionnaire is intrusive, long, and not suitable for weekly use *(73)*. We also use a seven-point Global Impression of Change (very much worse, much worse, a little worse, no change, a little better, much better, and very much better). Many authors use a visual analog scale.

OTHER TREATMENT MODALITIES

There are many causes of chronic pelvic pain *(74–76)*. Patients with pudendal neuralgia often have conventional diagnoses such as levator ani syndrome, pelvic floor tension myalgia, proctitis fugax, vulvodynia, interstitial cystitis, prostadynia, prostatitis, and sports hernia *(77,78)*. Previous therapies include phytotherapy, biofeedback, pelvic floor myofascial release, piriformis stretches and release, Kegel's exercises, magnetic therapy, microcurrent therapy, acupuncture, Botox injections, sacral nerve root stimulators, and surgeries, including pelvic exenteration *(79)*. Extensive research will be necessary to determine whether any of these diagnoses and treatments are associated with pudendal neuropathy or affect pudendal neuropathy. Only then can we determine the role of these alternative diagnoses in the spectrum of symptoms and treatments of pudendal neuralgia.

Confounding Neuropathies

Perry describes multiple neuropathic causes of pelvic pain in females *(80)*. Ilioinguinal neuropathy at its interdigitation in the inguinal and crural areas aggravates pudendal neuropathy. Genitofemoral neuropathy borders the pudendal distribution and may cause vexatious scrotal pain *(81–83)*. The pudendal nerve territory can extend into the abdomen and inguinal regions as shown in Fig. 7. The ventral axial line is shifted proximally and laterally as outlined by skin markings at limits of anesthesia following PNPI.

Middle cluneal neuropathy is a clinical entity that is common but essentially unknown to physicians. Often, it is caused by a "back mouse" or episacroiliac lipoma *(84)*. This is a fatty mass penetrating through the sacrospinalis fascia. It compresses the middle cluneal nerve against the skin or fascia *(85,86)*. The middle cluneal nerves are the posterior rami of S 2, 3, and 4. Symptoms may be remarkably similar to pudendal neuropathy and often include leg and foot pain. Injection of these nerves may completely relieve persistent postoperative pudendal neuropathic pains (Fig. 8).

Abdominal cutaneous nerve entrapment will obfuscate the clinical evaluation when inguinal or suprapubic pains are a clinical complaint. Recognition of this problem and treatment with local anesthetic blocks may be diagnostic and curative *(87)*.

Posterior Femoral Cutaneous Neuropathy

At surgery, the posterior femoral cutaneous nerve (PFCN) may be adjacent to the trunk of the pudendal nerve and suffer significant compression (FIGURE 4). PFCN neuropathy is suspected when "hamstring pain" accompanies pudendal neuropathic symptoms and responds to pudendal block where the anesthesia extends to the posterior thigh.

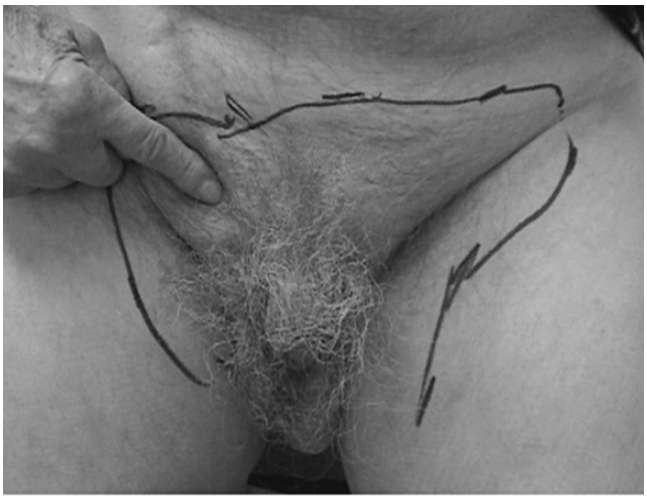


Fig. 7. Bilateral inguinal and suprapubic anesthesia 2 hours after transgluteal pudendal nerve blocks using bupivacaine 0.25% 6 ml and triamcinolone 40 mg, 1 ml. Anesthesia extends to medial upper thigh. Index finger touches site of subjective pain relieved by the pudendal block.

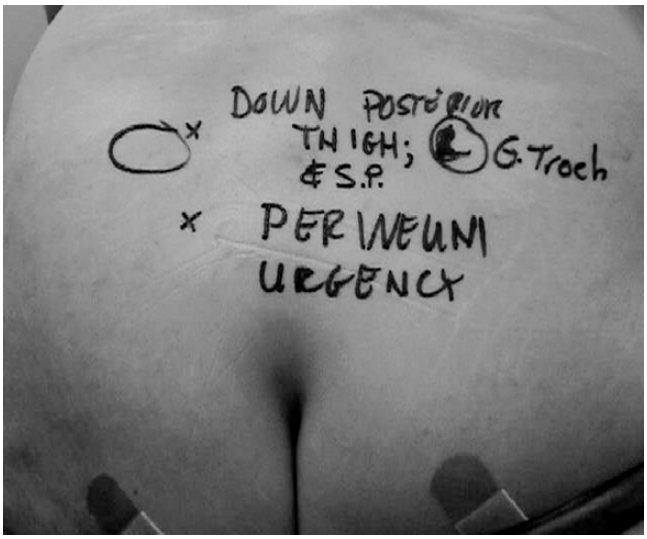


Fig. 8. A left-side, 2×4 cm subcutaneous fatty mass (back mouse) or episacroiliac lipoma at the S-2 level. Pressure at the sacral border causes pain in the posterior thigh, suprapubic area, and left greater trochanteric region. Pressure at S-4 level causes perineal pain and bladder urgency. This suggests spinal cord wind-up or central sensitization.

CONCLUSION

Multiple publications during the past two decades discuss the role of pudendal neuropathy in chronic pelvic pain, sexual dysfunction, and urinary and fecal incontinence. Recent case series consistently identify the symptom complex and treatment options for pelvic pain due to pudendal neuralgia. It is a compression or stretch

neuropathy of the pudendal nerve, a tunnel syndrome. Simple, effective testing is available to the practicing physician. Successful treatments are available. Confounding neuropathic processes in the inguinal region can be distinguished. We envision an intensive research effort to correlate the symptom variations of somatic pain, autonomic dysfunction, and motor dysfunctions with standardized neurophysiological testing and internationally accepted symptom scores. Surgical procedures need rigorous controlled studies to determine which is most efficacious. Physician awareness of neuropathic pelvic pain is of paramount importance. Only when early diagnosis is made can we prevent the serious compression neuropathy that is commonly found at surgical decompression.

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4 Dermatological Diseases Affecting the Genitourinary System

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Summary

Skin diseases of the male genitalia represent a diverse spectrum of maladies. Most cases fall into the differential diagnosis: fixed drug eruption, allergic/irritant contact dermatitis, infection, neoplasia/tumor, papulosquamous/systemic, and balanitides. A thorough history and physical examination defining the primary lesion, secondary changes, and distribution will establish most cutaneous diagnoses.

Key Words: Male genitalia; Skin disease; Intertrigo; Fixed drug eruption; Contact dermatitis; Infection; Neoplasia; Trauma; Papulosquamous dermatitis; Balanitis.

Contents

INTRODUCTION

Skin disease of the male genitalia can occur as a primary process for certain dermatoses with a predilection for the area, as an extension of generalized skin disease, or as an expression of systemic disease. A differential diagnosis can be broad but most diseases fall into one of the following categories: *fixed* drug eruption, *allergic*/irritant

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contact dermatitis, *infection, neoplasia*/tumor, *trauma*, papulosquamous/systemic, and balanitides, all of which can be recalled with the mnemonic F.A.I.N.T plus papulosquamous balanitis *(1)*.

Balanitis, inflammation of the glans penis, and posthitis, inflammation of the prepuce, can occur independently or together. Inflammation can also affect the scrotum, upper inner thighs, inguinal folds, perianal area, buttocks, and intergluteal folds. Inflammation of the skin folds, where skin surfaces meet, for example, upper inner thighs, perineum, intergluteal folds, and so on, is termed intertrigo.

A thorough history and physical examination establish most cutaneous diagnoses, confirmed, where appropriate, by laboratory tests. The history should include onset, symptoms, prior occurrence, current therapy, sexual practices, medications, allergies, and a review of systems. Physical examination should define the primary lesion, for example, papule, plaque; secondary changes, for example, erosion, ulcer; pattern; and distribution.

INFLAMMATORY DISEASES

Contact/Irritant Dermatitis

Contact dermatitis of the genitals can be allergic or irritant in nature. Common causes of allergic contact dermatitis include condoms, diaphragms, spermicides, lubricants, feminine hygiene products, and topical medicaments. Sensitivity to industrial or other contactants, for example, plant allergens, may produce contact sensitization on the groin through "hand transfer" *(1)*. Affected patients usually have sharply demarcated, red, edematous plaques on the glans and shaft, occasionally on the thighs and scrotum as well, and penile edema may be marked. Most patients experience some discomfort, usually pruritus and burning (See Fig. 1 and Color Plate 12, following p. 132).

Contact dermatitis associated with condoms and rubber diaphragms produces well demarcated, red plaques on the glans and shaft from exposure to tetramethylthiuram, mercaptobenzothiazole, and dithiocarbamate, the most common allergens in those products *(2,3)*. Patients allergic to tetramethylthiuram and mercaptobenzothiazole should use Trojan brand condoms or nonrubber condoms made from sheep intestine despite their questionable ability to prevent sexually transmitted diseases *(4,5)*.

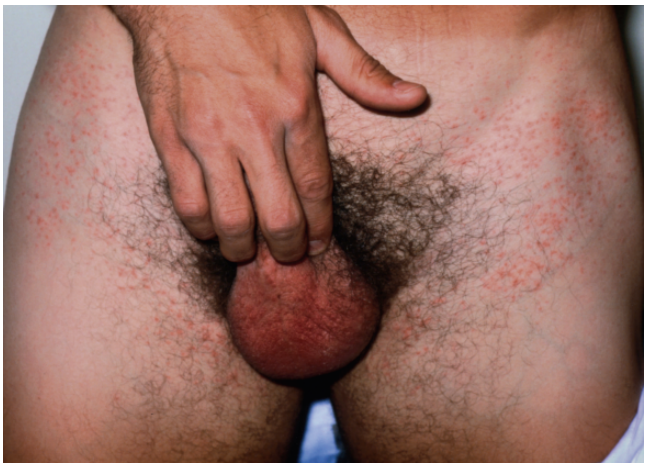

Fig. 1. Contact dermatitis (*see* Color Plate 12, following p. 132)

Other causes of contact dermatitis include condom lubricants, anesthetics within some condoms, for example, Benzocaine, feminine hygiene deodorant *(2,4,6)*, topical corticosteroids, topical antibiotics, and other topical medicaments, for example, diphenhydramine hydrochloride *(1,7)*. Propylene glycol is the common allergen in KY Jelly and parabens in other lubricants *(7)*. For allergic patients, alternative products include Surgilube, an aqueous-based lubricant without propylene glycol, and Trojan-Plus and Ramses condoms which contain nonsensitizing silicone-based lubricants *(1)*.

Rhus dermatitis can affect the genitals. The Rhus (Toxicodendron) family, which includes poison ivy, oak, and sumac, contains potent urshiol, commonly transferred to the genitals by the hand through contact sensitization to yield itchy, eczematous plaques and papules within 48 h after exposure. Skin disease may evolve over 2–3 weeks through latent transfer of the oil allergen embedded under the fingernails, clothing, and even from transfer of the allergen from pets that had contact with the urshiol.

Affected/exposed patients should wash thoroughly with soap and water within 30–60 min after plant contact, and clothing should be removed and laundered. Treatment typically requires the use of topical corticosteroids, compresses two to three times per day, and perhaps antihistamines for the itch. If disease is severe or widespread, systemic corticosteroids usually provide good relief, for example, prednisone 40 mg/day with a 3-week taper.

Irritant contact dermatitis is a common cause of chronic and recurrent balanitis, invariably the result of physical or chemical damage to the skin. Common culprits are detergents and soaps, less so antiseptics and disinfectants, often used as an attempt to prevent sexually transmitted disease *(8)*. A history of atopy and frequent washing of the genitals with soap can aggravate or induce balanitis *(9)*. In circumcised infants, urine is a common cause of irritant dermatitis because of the prolonged exposure to ammonia in the diapers *(10)*. Affected patients, regardless of age, typically have red, edematous plaques at the site of contact. With chronic dermatitis, lichenified, hyperkeratotic plaques develop.

Treatment of contact dermatitis requires elimination of the offending agent, application of a topical corticosteroid two to three times per day, and symptomatic treatment. If the contact allergen is unknown, patch testing may be helpful.

Lichen Simplex Chronicus

Lichen simplex chronicus (LSC) is a common chronic dermatitis in which itching is disproportionate to the dermatitis. LSC is characterized by dry, thickened, lichenified plaques produced by frequent rubbing or scratching. The inciting event is often an insect bite, contact dermatitis, localized infection, or other type of inflammation. Occasionally, LSC is purely psychologic with a continuous, paroxysmal or spasmodic cycle of pruritus, often severe and intractable, plus scratching. Itching tends to be worse at night, and disease is more common in older adults, especially women *(11)*. The childhood version is more common in boys and atopy can be a predisposing factor *(11)*.

LSC typically affects the scrotum but may extend to the shaft of the penis, the pubic area, perianal area, and inguinal folds. With persistent disease, hypopigmentation and/or hyperpigmentation can occur—hyperpigmentation by inflammation and hypopigmentation by scratching and rubbing, which leads to dysfunction, destruction, or mechanical removal of melanocytes *(11)*. Chronic and vigorous scratching, rubbing, and gouging can produce architectural changes of the anatomy. Heat, sweat, local infection, folliculitis, contact irritants, including clothing and medicaments can exacerbate the itch *(11,12)*.

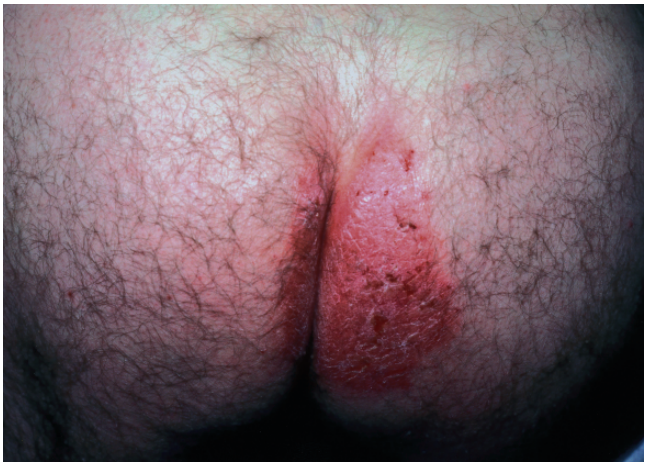

Fig. 2. Lichen simplex chronicus (*see* Color Plate 13, following p. 132)

Treatment includes identification and treatment of any primary skin disease, that is, contact dermatitis, infection, and so on; grouped with reconstitution of barrier function through compresses, colloidal oatmeal baths, and emollients; and the use of topical corticosteroids to reduce inflammation and break the itch–scratch cycle. For some patients, the use of a tricyclic antidepressant may be necessary *(11,12)* (See Fig. 2 and Color Plate 13, following p. 132).

Factitial Disease and Trauma

Trauma to the male genitals includes automobile accidents, gunshot wounds, burns, crush injuries, frostbite, suction/vacuum erection devices, penile tourniquet syndrome, amateur circumcision, zipper entrapment, and rigorous sexual activity, that is, intercourse or masturbation, all of which can have devastating sequelae. Many traumatic events are self-induced *(1,13,14)* (See Fig. 3 and Color Plate 14, following p. 132).

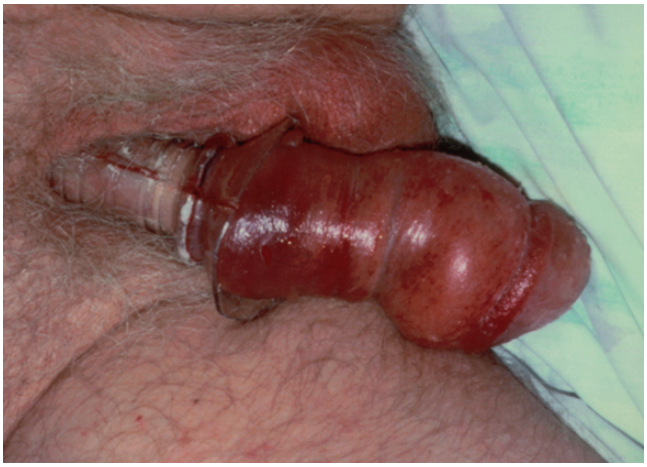

Fig. 3. Factitial trauma (*see* Color Plate 14, following p. 132)

Vacuum cleaner injury, amateur circumcision, insertion of an electric drill, machinery injury, and zipper entrapment produce self-induced lacerations *(13,15–18)*. Penile tourniquet syndrome usually occurs in boys when a human hair, hidden in the coronal sulcus, encircles the penis, causing pain, swelling, and erythema of the glans, which can ultimately lead to urethral fistula and amputation of the glans *(19,20)*. Diagnosis and treatment may be difficult, especially if guilt, embarrassment, or psychiatric disturbances delay medical attention.

Factitial dermatitis (dermatitis artefacta) is self-inflicted, often mutilating disease characterized by cuts, excoriations, sharply demarcated ulcers, and even gangrenous wounds created by picking, rubbing, biting, scratching, or by cutting with knives or scissors, burning with matches, or applying chemical/caustic irritants.

The pattern, distribution, and morphology of the skin disease suggest the diagnosis—geometric arrangement, sudden appearance of "lesions," resistant "lesions," "lesions" surrounded by normal skin, and disease only in "reachable areas." Therapy can be difficult, especially if patient insight is poor. Occlusive dressings, especially for extremity disease, can be very helpful, coupled with the use of emollients and topical corticosteriods. Most patients deserve psychiatric evaluation and therapy, but many resist the advice.

Psoriasis

Many skin diseases affect the male genitalia, for example, psoriasis, lichen planus (LP)/nitidus, seborrheic dermatitis, pemphigus vegetans, and erythema multiforme. Psoriasis and LP characteristically occur on the glans and may not occur elsewhere. Crohn's disease, ulcerative colitis, Behcet's disease, and Reiter's disease can affect the area as well *(1)* (See Fig. 4 and Color Plate 15, following p. 132).

Psoriasis is the most common inflammatory disorder of the male genitalia affecting men of all ages *(21)*. Unlike the classic appearance of scaly, red plaques, genital psoriasis typically exhibits nonscaly, pink/red plaques, especially in intertriginous areas and on the prepuce and glans penis. Classic psoriatic plaques elsewhere, that is, scalp, elbows, and knees, help to confirm the diagnosis. Penile psoriasis is usually asymptomatic except for increased sensitivity at the site during intercourse.

Trauma to the genitalia can produce koebnerization, development of psoriatic disease at the site. First-line therapy is a topical corticosteroid applied two to three times per day, or, alternatively, calcipotriene cream as a steroid sparing agent though irritant contact dermatitis can develop *(8)*. Affected patients should wear loose-fitting underwear with attention to good hygiene. For widespread disease, therapy with either methotrexate, acitretin (Soriatane), or one of the new biologics may be helpful.

Lichen Planus/Nitidus

LP is an inflammatory disease characterized by violaceous, flat, itchy papules with fine, white reticulated pattern (Wickham's striae) that are typically located on the flexor aspects of the arms and legs. LP affects less than 1% of the population, primarily middle-aged adults *(22,23)*, but 25% of affected patients have genital disease and the genitalia may be the only affected area *(24)*. In men, LP occurs on the glans penis, less so on the shaft, scrotum, and perineum (See Fig. 5 and Color Plate 16, following p. 132).

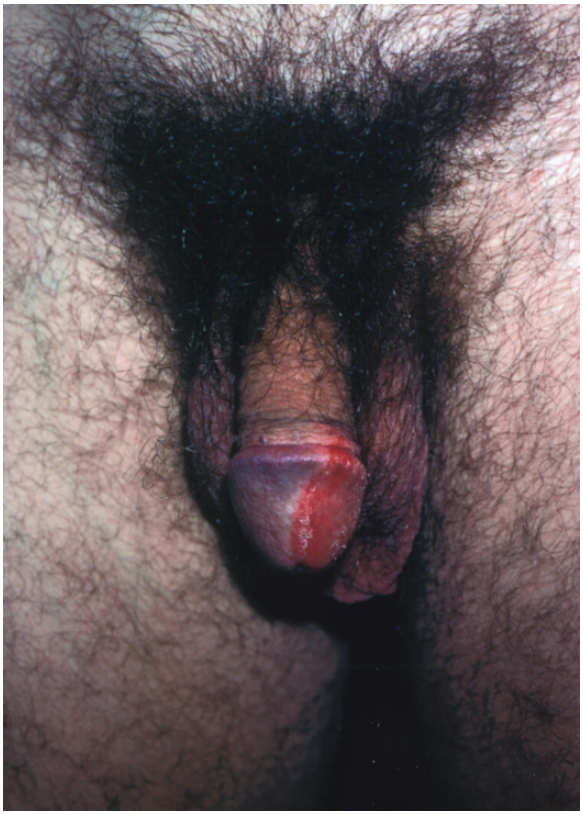

Fig. 4. Psoriasis (*see* Color Plate 15, following p. 132)

Genital morphology varies from polygonal papules to annular plaques, and occasionally erosions, that is, erosive LP, which may develop into squamous cell carcinoma (SCC) *(25,26)*. Symptoms of genital disease include pruritus, burning, and dyspareunia.

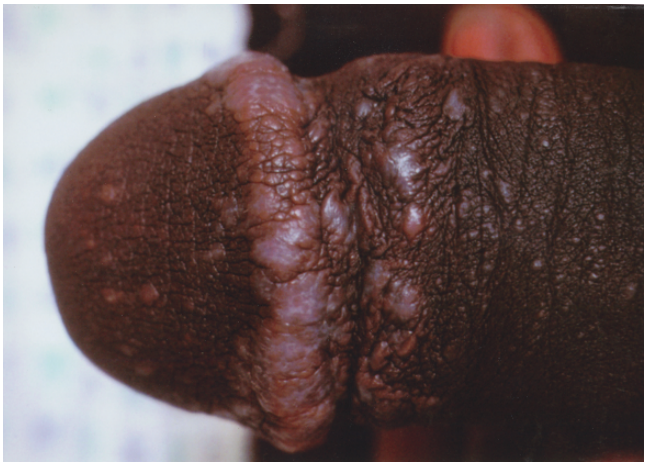

Fig. 5. Lichen planus (*see* Color Plate 16, following p. 132)

LP usually resolves spontaneously in 1–2 years. Localized disease is treated with topical corticosteroids but systemic corticosteroids may be necessary for extensive disease.

Lichen nitidus (LN) is an uncommon inflammatory disorder characterized by small, grouped, monomorphous, flesh-colored/shiny papules on the penis, arms, forearms, elbows, knees, and abdomen. Pruritus is usually absent or mild, and the papules usually resolve within several months though disease may persist indefinitely. LN primarily affects children and young adults; its cause is unknown *(23)*. Therapy may not be necessary, but topical corticosteroids can help the appearance and itch *(23)* (See Fig. 6 and Color Plate 17, following p. 132).

Balanitis Xerotica Obliterans

Balanitis xerotica obliterans (BXO) is a chronic inflammatory disease characterized by white, atrophic plaques on the glans penis, prepuce, and urethral meatus. Vesicles, hemorrhage, edema, and ulceration may develop, especially after trauma. With progressive disease, phimosis and urethral stenosis can occur. The etiology is unknown, but it may be an expression of lichen sclerosus et atrophicus. Some patients with BXO have developed SCC, which emphasizes the need for regular evaluation and biopsy if warranted *(27,28)* (See Fig. 7 and Color Plate 18, following p. 132).

BXO usually occurs in the fourth and fifth decades, usually with insidious onset *(29)*. Most patients have pain, pruritus, or burning or stinging at the site; others have phimosis, dysuria, or voiding difficulties. In one study, urethral discharge was the presenting problem *(29)*.

First-line therapy is application of a topical corticosteroid coupled with liberal use of emollients, alternatively, intralesional corticosteroids. Laser vaporization has been successful in some patients. Phimosis requires circumcision *(30–32)*. Meatotomy, meatoplasty, or urethroplasty may be necessary for patients with urethral stenosis *(33)*.

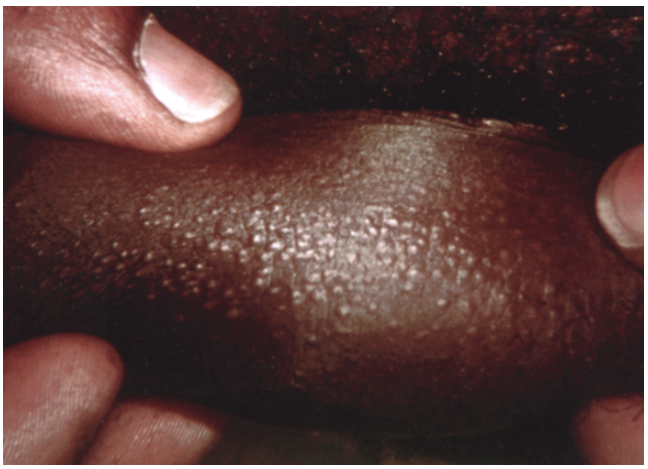

Fig. 6. Lichen nitidus (*see* Color Plate 17, following p. 132)

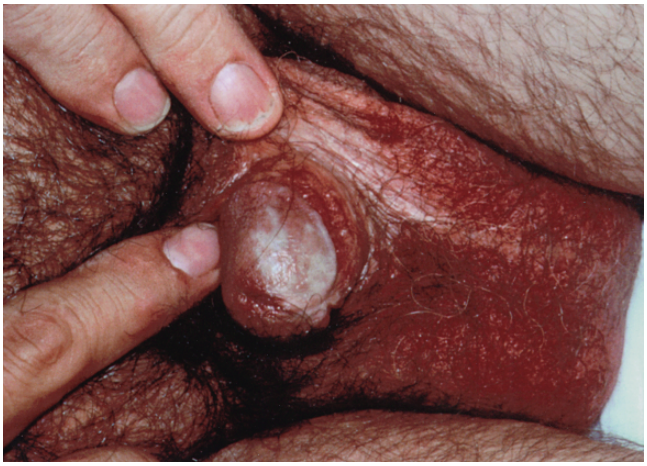

Fig. 7. Balanitis xerotica obliterans (*see* Color Plate 18, following p. 132)

Plasma Cell Balanitis

Plasma cell balanitis is a persistent, shiny, red plaque with "cayenne pepper" spots on the glans penis, coronal sulcus, or mucosal surface of the prepuce in older, uncircumcised men. Affected patients are usually asymptomatic, but burning, tenderness, or pruritus can occur. The etiology is unknown, but it may follow infection with *Mycobacterium smegmatis* or human papilloma virus. Predisposing factors include repeated infections, heat, occlusion, constant friction, and poor hygiene *(34–36)*.

Plasma cell balanitis must be differentiated from Erythroplasia of Queyrat (EQ) and SCC. Biopsy helps to differentiate the entities (See Fig. 8 and Color Plate 19, following p. 132).

Treatment is circumcision. Other, less effective therapies include topical and intralesional corticosteroids, cryosurgery, and carbon dioxide laser therapy *(34,35)*.

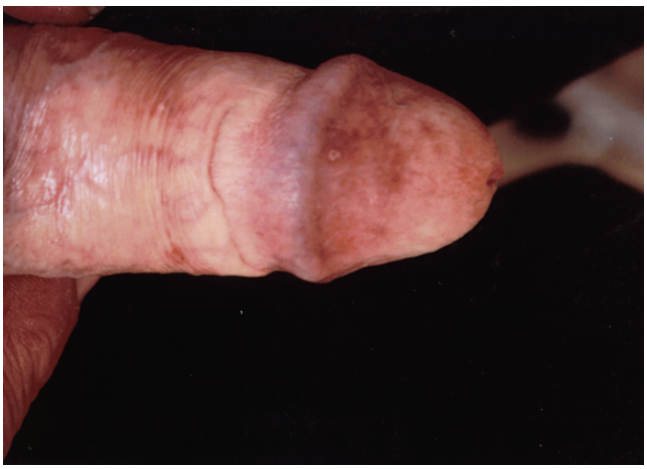

Fig. 8. Plasma cell balanitis (*see* Color Plate 19, following p. 132)

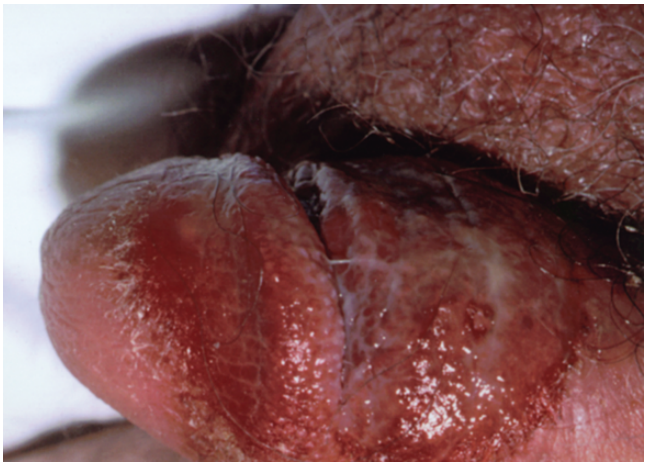

Fig. 9. Fixed drug reaction (*see* Color Plate 20, following p. 132)

Fixed Drug Eruption

Fixed drug eruption is a common hypersensitivity reaction to medications characterized by a well-defined, red-brown plaque which often develops on the penis, less so on the perianal area, lips, hands, or feet. Occasionally, a bulla may appear within the plaque. Affected patients may experience burning/stinging, pain, or pruritus at the site as well as malaise, fever, chills, nausea, and vomiting; necrosis and ulceration are rare *(37,38)* (See Fig. 9 and Color Plate 20, following p. 132).

The plaque usually resolves in 2–3 weeks after discontinuation of the medication followed by hyperpigmentation which is often persistent. Repeated exposure to the offending drug induces the same reaction in the same location, hence the name. Common offending medications are tetracycline, phenolphthalein, barbiturates, trimethoprim–sulfamethoxazole, and penicillins *(39,40)*.

Therapy is twofold – discontinuation of the offending medication and the application of a topical corticosteroid *(40)*.

INFECTIONS

Infections of the male genitalia and surrounding area are common and plentiful. Dermatologically, candidal infections are most common, less so dermatophyte infections, histoplasmosis, blastomycosis, cryptococcosis, and *Penicillicum* infection; bacterial infections, that is, Streptococci, Staphylococci, Chlamydia, Neisseria, and Treponema; parasitic infections, that is, entamoeba, trichomonas, sarcoptes, and leishmania; and viruses, that is, herpes, human papillomavirus, and pox virus. Common selected infections follow; others are covered elsewhere in this book *(1)*.

Candidiasis

Candida albicans is a common cause of balanitis and intertrigo. Asymptomatic penile carriage rate is 15–20% and even higher in uncircumcised men *(41)*. Candidal

balanitis occurs primarily in uncircumcised men, accounting for 30–35% of all cases of infectious balanitis *(42,43)*. Risk factors include trauma, obesity, phimosis, incontinence, advanced age, malnutrition, warm, moist environment, recent use of oral antibiotics, diabetes, poor hygiene, and intercourse with women with candidal vulvovaginitis *(44,45)*. Glazed, red plaques with gray-white curdlike deposits on the prepuce or penis suggest the diagnosis. Secondary changes include erosions, exudation, and maceration. Pruritus and burning are common complaints, and ulceration and phimosis can occur as an extension of severe disease. Presence of pseudohyphae on potassium hydroxide (KOH) preparation establishes the diagnosis. Treatment includes good hygiene, often with compresses three to four times per day initially, followed by application of a topical antiyeast cream, for example, clotrimazole or econazole two to three times/day for 2–3 weeks. For extensive or persistent disease, fluconazole, 150 mg, as a single dose is very beneficial *(10,46)* (See Fig. 10 and Color Plate 21, following p. 132).

Candidal intertrigo occurs almost exclusively in obese individuals. Other risk factors include debilitation, incontinence, diabetes, hypothyroidism, malignancy, immunosuppression, hyperhidrosis, advanced age, and terminal illness *(12)*. Candidal intertrigo is typically a red, macerated plaque with "satellite pustules" in the skin folds, that is, axillae, groin, and beneath breasts. Presence of budding yeasts and pseudohyphae on KOH preparation establishes the diagnosis.

Treatment is aeration, coupled with the use of an azole or nystatin cream applied one to two times daily to the affected area for 2–3 weeks. For extensive or resistant disease, fluconazole, 100 mg/day, is very beneficial *(47)*. Regular washing of the affected areas, with thorough drying and aeration, plus light, loose, nonconstricting clothing help to prevent recurrence. For obese patients, weight loss is mandatory to offset recurrences *(44,47,48)*.

Tinea Cruris

Dermatophyte infections are common in the general population. Causative organisms are *Trichophyton, Epidermophyton*, and *Microsporum* species. Tinea cruris ("jock itch") is a common infection of the groin characterized by well-defined, annular, scaly

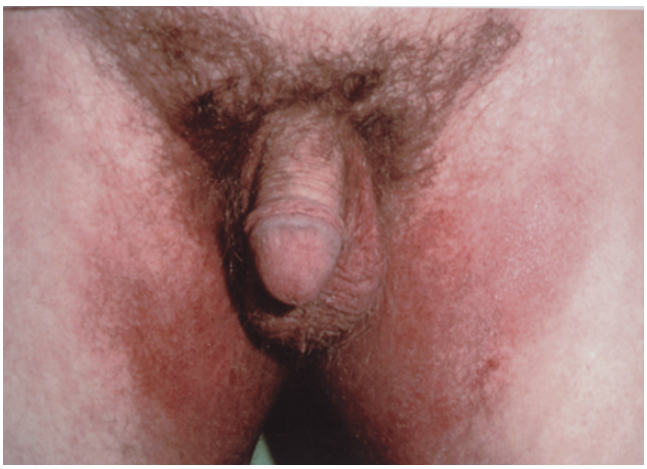

Fig. 10. Candidiasis (*see* Color Plate 21, following p. 132)

plaques, which may extend to the perianal area and upper, inner thighs. *Trichophyton rubrum* is the most common pathogen of tinea cruris, less so *trichophyton mentagrophytes* and *epidermophyton floccosum*. Plaques are usually bilateral and symmetric and spare the penis and the scrotum in contrast to candidiasis. *Tinea cruris* primarily affects men, and concomitant infections of the feet are common *(49)* (See Fig. 11 and Color Plate 22, following p. 132).

Predisposing factors for tinea cruris include obesity, hyperhidrosis, impaired immunity, occlusive clothing, and contact sports. A KOH preparation from the scaly edge of the plaque should reveal branching hyphae to establish the diagnosis. Treatment with an antifungal cream, for example, an azole, allylamine, benzylamine, or hydroxypyridone, one to two times daily for 2–3 weeks, usually eradicates the problem *(50,51)*. Additionally, patients should employ good hygiene, coupled with use of light, loose-fitting undergarments, and should refrain from sharing towels and undergarments with others. For extensive disease, recurrent infection, or for immunocompromised patients, systemic therapy may be warranted, either terbinafine 250 mg/day for 1–4 weeks, fluconazole 150–300 mg/week for 2–4 weeks, or itraconazole 100–200 mg/day for 1–2 weeks *(50,51)*. For excessive exudative disease, compresses two to three times per day, with aluminum acetate or potassium permanganate solution, are helpful to promote drying.

Erythrasma

Erythrasma is a superficial intertriginous infection caused by *Corynebacterium minutissimum*, a gram-positive bacillus and part of the normal skin flora. Characterized by a poorly demarcated, red-brown plaque in the inguinal area, the axillae, inframammary areas, or intergluteal fold, erythrasma is usually asymptomatic and occurs primarily in men, occasionally compounded by a warm climate, advanced age, and diabetes mellitus *(52)*. Wood's light (dark light) examination reveals coral-red fluorescence establishing the diagnosis (See Fig. 12 and Color Plate 23, following p. 132).

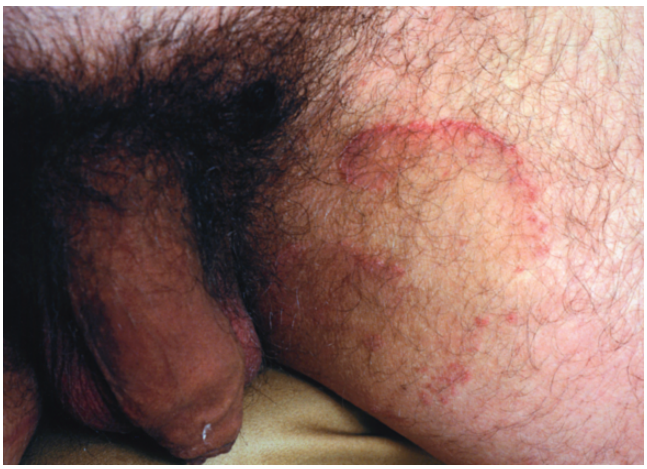

Fig. 11. Tinea cruris (*see* Color Plate 22, following p. 132)

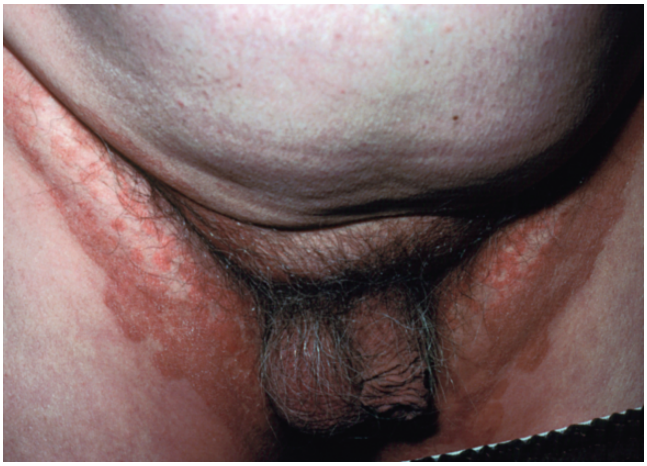

Fig. 12. Erythrasma (*see* Color Plate 23, following p. 132)

Erythrasma can resemble tinea cruris, and concurrent dermatophyte or candidal infection can occur. Therapy for erythasma is erythromycin 250 mg four times daily for 14 days or clindamycin solution or erythromycin solution applied twice per day for 2 weeks *(52)*. Despite therapy, recurrence is common.

Hidradenitis Suppurativa

Hidradenitis suppurativa (HS) is a disease of follicular hyperkeratosis and resultant occlusion and rupture of the hair follicle, often with secondary inflammation and occasionally bacterial infection *(53–55)*. HS is characterized by tender nodules and draining abscesses, sinus tracts, and scarring and affects the axillae, inguinal and anogenital areas, and inframammary areas (women). Chronic, recurrent disease is the usual pattern. The etiology is unknown, but disease typically affects obese women and perianal disease is more common in men. The exact incidence of HS is unknown

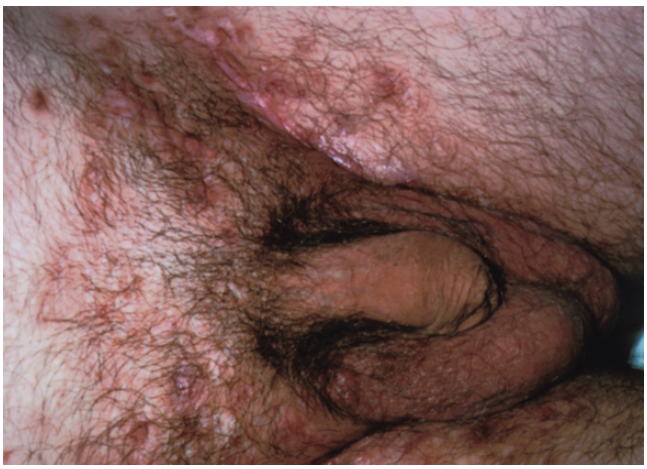

Fig. 13. Hidradenitis suppurativa (*see* Color Plate 24, following p. 132)

but estimates indicate that 1 in 300 adults are affected, and 26% of patients have an affected family member *(53,56)* (See Fig. 13 and Color Plate 24, following p. 132).

First-line therapy includes warm compresses two to three times per day, daily cleansing with an antiseptic soap, for example, chlorhexadine (Hibiclens), and oral antibiotics, usually tertracycline, 500 mg twice per day, or doxycycline, 100 mg twice per day. Some patients require excision of the apocrine gland-bearing tissue as definitive therapy *(57)*. For obese patients, weight loss is essential. Sequelae include fibrosis, contractions, scarring, fistula formation, and, rarely, the development of SCC *(57)*.

COMMON BENIGN GROWTHS

Pearly Penile Papules

Pearly penile papules (PPP) most commonly occur in teenagers and young men. PPP typically occur on the corona sulcus of the penis in a single or double row, can encircle the corona partially or completely, occasionally cover the glans penis, and even appear ectopically on the penile shaft. Papules are asymptomatic, dome shaped, and small (1–2 mm) with pink, white, or translucent color. They can vary in shape, size, and color from person to person but are uniform for a given individual. Prevalence ranges from 14.3 to 48%, and incidence decreases with age *(58)*. Most patients seek medical attention because they are concerned about sexually transmitted diseases. PPP can resemble condyloma acuminatum. Therapy is not necessary (See Fig. 14 and Color Plate 25, following p. 132).

Angiokeratoma of Fordyce

Angiokeratomas are a superficial proliferation of dermal blood vessels that appear as dark red or black papules. Several types exist: angiokeratoma circumscriptum, angiokeratoma of Fordyce (genital), angiokeratoma of Mibelli, solitary angiokeratomas, and widespread angiokeratomas of systemic diseases. Angiokeratoma of Fordyce is the most common type, appearing on the vulva and scrotum most often, and less so on the

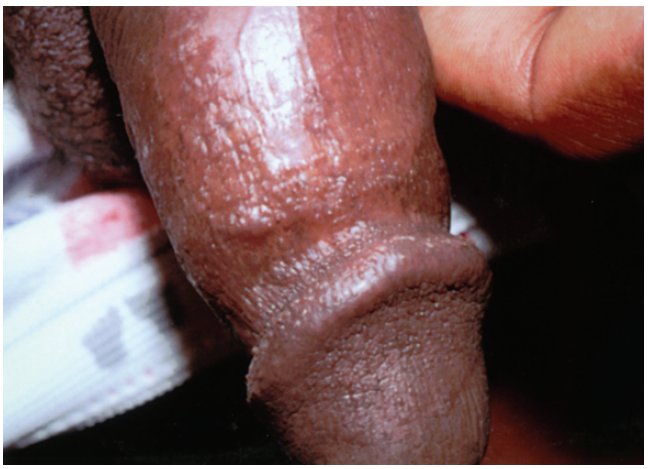

Fig. 14. Pearly penile papules (*see* Color Plate 25, following p. 132)

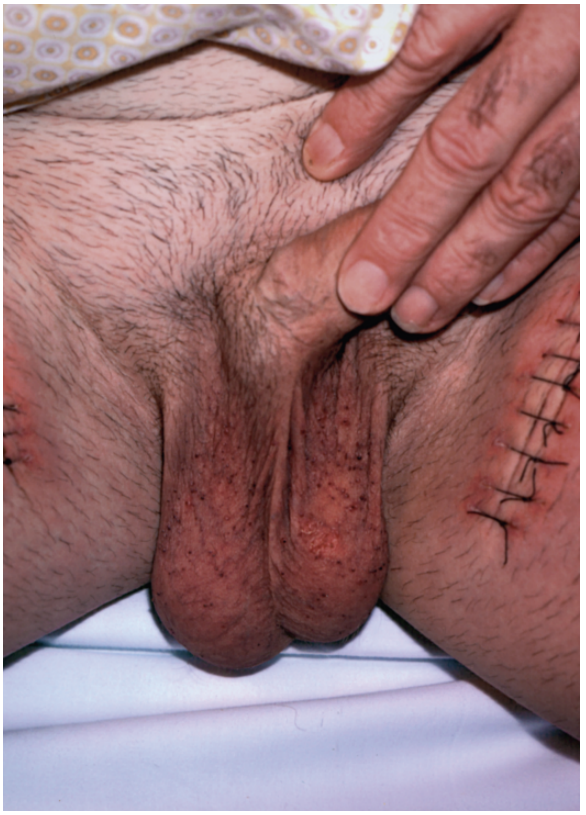

Fig. 15. Angiokeratoma (*see* Color Plate 26, following p. 132)

penis. Some patients may have hundreds of such papules *(59)*. Angiokeratomas occur in adults, occasionally in association with varicocele, inguinal hernia, or thrombophlebitis. Bleeding, with or without trauma, may occur (See Fig. 15 and Color Plate 26, following p. 132).

Angiokeratomas do not require therapy per se, unless persistent bleeding or discomfort occurs. If so, excision, cryotherapy, or cautery is usually effective *(60,61)*.

Idiopathic Calcinosis of the Scrotum

Idiopathic scrotal calcinosis describes asymptomatic, pale or yellow-white papules on the scrotum, which may be single or multiple, but can increase in number to produce scrotal deformity. Most are painless, but some discharge a chalky white material. The calcinosis occurs in boys and young men and tends to persist indefinitely *(62,63)*. Affected patients have normal serum and urinary levels of calcium, phosphate, and uric acid *(64)*. If warranted, surgical excision is usually curative.

MALIGNANT GROWTHS

Primary cancers of the male genitalia include EQ, SCC, verrucous carcinoma, basal cell carcinoma, melanoma, Kaposi's sarcoma, extramammary Paget's disease, and micaceous and verrucous malignant balanitis. Metastases from genitourinary and gastrointestinal cancers often occur on the genitalia. Primary tumors may exhibit a

number of secondary changes including pruritus, pain, erythema, blistering, ulceration; occasionally even hematuria, dysuria, discharge, and phimosis occur *(1)*.

Squamous Cell Carcinoma

EQ, or SCC in situ, is a precancerous plaque that may evolve into an invasive SCC. Ulceration can herald such transformation. EQ affects primarily uncircumcised men in the fifth decade or later *(65)*. Plaques are usually moist, erythematous, and well-circumscribed, covering the glans or mucosa of the prepuce or both; they may be solitary or multiple. The plaques are usually symptomatic—they itch, hurt, or bleed and retraction of the foreskin may be difficult and/or painful. Human papilloma virus and chronic irritation from poor hygiene, retained smegma, friction, and trauma may be causative or aggravating factors *(65–68)* (See Fig. 16 and Color Plate 27, following p. 132).

Biopsy establishes the diagnosis. Treatment depends on the location and size of cancer and includes circumcision, cryosurgery, and Mohs micrographic surgery *(65, 67,69,70)*.

Penile carcinoma is rare in the USA but accounts for 10–20% of all cancers in men elsewhere, especially in South America, Asia, and Africa *(71,72)*. SCC is the most common type, representing approximately 95% of all penile malignancies, with 60 as the mean age at diagnosis *(71)*.

Penile carcinoma may occur anywhere on the penis, but 60% of cancers occur on the glans, the prepuce, or both *(73)*. Most are either ulcerated plaques or verrucous/exophytic plaques with a tendency to ulcerate and become necrotic. Patients usually experience pruritus, burning, bleeding, difficulty voiding, phimosis, discharge, and/or pain at the site. Lymphadenopathy occurs with advanced disease, affecting approximately 50% of patients at the time of diagnosis *(73)*.

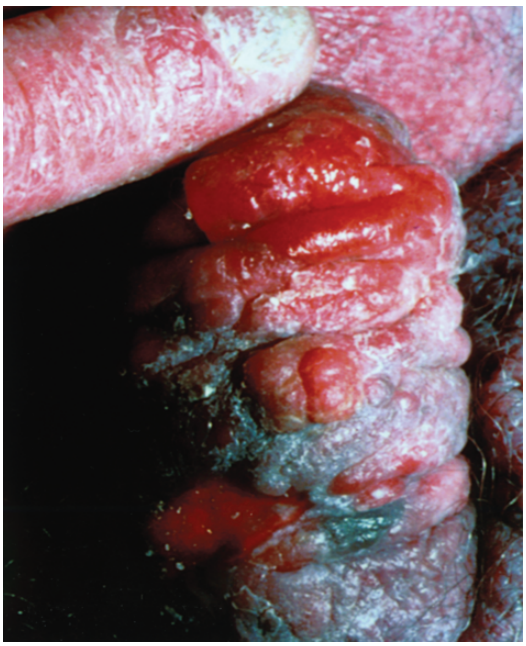

Fig. 16. Squamous cell carcinoma (*see* Color Plate 27, following p. 132)

Risk factors for penile cancer include history of smoking or treatment with psoralen, genital warts, phimosis, multiple sexual partners, uncircumcised state, circumcision after infancy, and perhaps BXO (lichen sclerosis), though rarely so *(1,27,74–76)*. Penile carcinoma is very rare in circumcised men.

Detection and treatment of precancerous penile disease are the key to prevention of SCC. Once penile carcinoma develops, treatment options, depending on size, location, and stage at diagnosis, include wide excision, Mohs micrographic surgery, laser surgery, or radiation therapy *(1)*.

SCC of the scrotum is very rare in the USA; approximately 10 new cases occur each year *(77)*. Incidence is high in Persian and Turkistan tribesmen and in industrial oil workers worldwide. Disease is strongly linked to chimney sweeping with evidence implicating the alkaline ether extract found in chimney soot. In tribesmen, the putative cause is the charcoal-filled pots carried underneath robes to keep warm, and in the industrial workers, industrial oils and their products. SCC of the scrotum is more common in urban men of lower socioeconomic class with poor hygiene *(78)*.

Scrotal SCC begins in the fifth or sixth decade as a papule or nodule that increases in size and eventually ulcerates *(79)*. Treatment is wide excision or Mohs surgery. Neither chemotherapy nor radiation therapy improves survival, which is poor. Most patients delay medical attention for 8–12 months by which time disease has spread to lymph nodes or elsewhere *(77)*. If localized to the scrotum, the long-term survival with excision is 70% *(79)*.

Extramammary Paget's Disease

The first case of extramammary Paget's disease (EMP) affecting the scrotum and penis was first described by Crocker in 1889 after Paget had described Paget's disease of the nipple 15 years earlier *(80)*. EMP is usually a solitary, well demarcated, reddened, eczematous plaque which may itch or burn *(80,81)*. Plaques may become verrucous or vegetative (See Fig. 17 and Color Plate 28, following p. 132).

EMP has a predilection for areas with apocrine gland concentration (50–80% of cases) or eccrine gland concentration *(80,81)*. Other sites include the vulva or

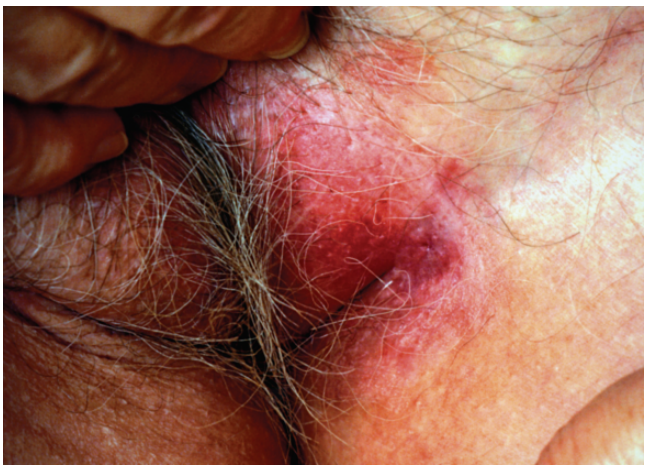

Fig. 17. Extramammary Paget's disease (*see* Color Plate 28, following p. 132)

anogenital region and uncommonly the axillae, eyelid, and external auditory canal. In the anogenitial region, disease primarily affects the perianal area though disease can be confined to the penis, scrotum, or groin, though rarely so.

EMP occurs more commonly in elderly patients, especially Caucasian women. Commonly associated with underlying malignancy (50%), either an underlying adnexal carcinoma or a visceral malignancy of the distal gastrointestinal tract or genitourinary tract, EMP has a poor prognosis *(81,82)*. Given the association, patients with EMP deserve rigorous evaluation for underlying gastrointestinal and genitourinary malignancy. EMP of the penis is specifically linked with genitourinary malignancy *(81)*.

Preferred therapy is Mohs micrographic surgery versus wide excision or laser surgery. Radiation is reserved for nonsurgical candidates *(83–87)*.

Melanoma

Melanoma rarely affects the penis or scrotum and represents only 1% of all penile malignancies. Most (66%) occur on the glans, and less frequently on the prepuce, urethral meatus, penile shaft, and coronal sulcus *(77,88–92)*. Melanoma of the scrotum is a rare manifestation of genitourinary melanoma *(93)*. On the genitalia, melanoma is usually an enlarging pigmented plaque, which often ulcerates or bleeds, with variegated color (blue-black, black, brown, or reddish-brown). Genital melanoma can occur at any age, but most often in the sixth or seventh decade *(90,94,95)*.

Melanoma with a Breslow depth of less than 0.76 mm has a negligible likelihood to metastasize. With increasing tumor thickness, 0.76–2.25 mm, 2.26–3.0 mm, and greater than 3 mm, the likelihood of metastasis increases—33, 69, and 84%, respectively *(96)*. Treatment is wide excision or Mohs micrographic surgery followed by adjunctive radiotherapy or chemotherapy for palliation. Lymph node resection remains controversial *(77)*. At the time of diagnosis, 60% of patients with genital melanoma have distant metastases *(88)*. Early diagnosis and surgical resection are essential for survival.

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5 Sexually Transmitted Infections

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Summary

Screening for sexually transmitted diseases is an essential form of secondary prevention. Physicians should construct a differential diagnosis for genital ulcers, urethritis, vaginitis, and other inflammatory disorders of the genitourinary tract with a higher index of suspicion for sexually transmitted diseases. The authors outline various sexually transmitted infections (STIs) and diseases and current recommended treatment options.

Key Words: Sexually transmitted disease; sexually transmitted infections genital ulcers urethritis vaginitis.

Contents

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INTRODUCTION

Primary prevention through universal safe-sex precautions would eliminate the costly and sometimes tragic consequences of sexually transmitted infections (STIs). However, because STI transmission remains prevalent, *secondary* prevention through screening and early diagnosis remains our most valuable weapon against the devastating disease sequelae.

Early detection and appropriate antibiotic therapy have led to decreases in bacterial venereal diseases. For example, the incidence of syphilis in the USA has decreased from 51,000 in 1990 to 8724 in 2005 *(1)*. Likewise, the incidence of gonorrhea has decreased from one million in 1980 to less than 340,000 cases documented in 2005 *(2)*.

Chlamydia trachomatis remains the most common reportable bacterial STI, with an estimated 2.8 million new cases in the USA each year and 50 million worldwide *(3)*.

Viral infections, for which curative therapy is not available, have been stable or increasing in prevalence. With 500,000 new cases each year, herpes simplex virus (HSV) is one of the most common viral STI. One million new cases of human papilloma virus (HPV) are diagnosed each year, and the prevalence of this disease is between 24 and 40 million.

People at high risk of contracting sexually transmitted diseases are young adults between the ages of 18 and 28. The highest rate of gonorrhea and chlamydia infections are among females aged 15–19 *(4)*. It is also important to bear in mind that sexually transmitted diseases rank among the top five risks of international travelers, along with diarrhea, hepatitis, and motor vehicle accidents *(5)*.

A urologist should have a high index of suspicion for underlying sexually transmitted disease in women who present with recurrent urinary tract infections (UTIs) and in those who are symptomatic with sterile urine cultures. Up to 50% of women with signs of UTI during emergency department examination had subsequent positive cultures for sexually transmitted disease *(6)*. Physicians should maintain the same level of vigilance when treating women who have sex with women. Genital HPV has been identified along with squamous intraepithelial lesions among lesbians and occurs among those who have not had sexual relations with men *(7)*. A high prevalence of bacterial vaginosis (BV) has been observed between monogamous lesbians. Because of more frequent orogenital practices, they may also be at higher risk of HSV type 1 *(4)*.

Proctitis may occur in women and men who have anal sex. Causative organisms include *Neisseria gonorrhoeae, C. trachomatis, Treponema pallidum*, and HSV. A discussion of human immunodeficiency virus (HIV) is beyond the scope of this chapter; however, it is important to remember that STI—especially the ulcerative types—facilitates the transmission and infection of HIV. HSV-2, in particular, may play a role in the transmission of HIV, as it has been identified more frequently than other STI among HIV-concordant couples *(8)*.

The most common sexually transmitted diseases are discussed in the following pages. They include HSV, chlamydia urethritis/cervicitis, lymphogranuloma venereum, syphilis, gonorrhea, chancroid, trichomoniasis, and HPV. Other sexually associated pathogens, which cause urethritis and vaginitides, will also be discussed briefly.

Expedited Partner Therapy

A common dilemma for physicians treating patients with an STI is how to expeditiously extend treatment to the partner to both prevent complications from infection,

such as pelvic inflammatory disease (PID), and prevent the spread of disease. Traditional methods of patient or physician referral have obvious benefits and limitations. Expedited partner therapy (EPT) is the practice of treating the sexual partners of patients with STI by providing the patient with a prescription or medication to take their partner without an intervening clinical evaluation or professional prevention counseling.

In August of 2006, CDC concluded that EPT has been shown to be at least equivalent to patient referral in preventing persistent or recurrent GC or chlamydial infection in heterosexuals and released guidelines for the uses of EPT [I]. The guidelines recommend that EPT should only be implemented when other management strategies are impractical or unsuccessful. All recipients should be encouraged to seek medical attention, in addition to accepting therapy by EPT, through counseling of the index case, written materials, and/or personal counseling by a pharmacist or other personnel. The CDC guidelines suggest that EPT may be used to treat GC and chlamydial infection in heterosexual women and men. It should not be used routinely in MSM because of a lack of data to confirm efficacy in this population and the high risk of co-morbidity, especially with undiagnosed HIV. Similarly, EPT should not be used for partners of women with trichomoniasis because of the high risk of co-morbidity with chlamydia or GC. EPT is not recommended for routine use in the management of patients with infectious syphilis.

To address legal and medicolegal status of EPT, CDC collaborated with the Center for Law and the Public's Health at Georgetown and Johns Hopkins Universities to assess the legal framework concerning EPT in all 50 states, the District of Columbia and Puerto Rico. The objective of the research was to conceptualize and identify legal provisions that implicate a clinician's ability to execute EPT. Currently, EPT is allowable in 11 states, potentially allowable in 28 states, and legally prohibited in 13 states. The results of the research, explanation, and legal status for each state can be found at the CDC website http://www.cdc.gov/std/ept/legal/default.htm.

EPT References

[I] Centers for Disease Control and Prevention. *Expedited Partner Therapy in the Management of Sexually Transmitted Diseases*. Atlanta, GA: US Department of Health and Human Services, 2006.

GENITAL ULCERS

Several STIs are clinically characterized by the genital ulcers typically associated with them, most commonly HSV, syphilis, and chancroid. In 2002, it was estimated that over 45 million persons had HSV while only 6862 cases of syphilis and 67 cases of chancroid were reported.

Although specificity for clinical diagnosis of genital ulcer disease is good (94–98%), sensitivity is quite low (31–35%) *(9)*. Inguinal lymph node findings did not contribute to diagnostic accuracy. Confirmatory cultures and serologic testing for syphilis, chancroid, and HSV should be performed whenever possible. Specifically, the CDC recommends (i) serology and either darkfield examination or direct immunofluorescence for *T. pallidum*, (ii) culture or antigen test for HSP, and (iii) culture for *Haemophilus ducreyi*. It should be kept in mind that patients may be co-infected with more than one sexually transmitted disease. Approximately 10% of patients with chancroid are co-infected with HSV or syphilis. HIV testing should be strongly considered in the

Table 1
Genital Ulcer Disease

Disease	*Lesions*	*Lymphadenopathy*	*Systemic symptoms*
Primary syphillis	Painless, indurated, clean-based, usually singular	Nontender, rubbery, nonsuppurative bilateral lymphadenopathy	None
Genital herpes	Painful vesicles, shallow, usually multiple	Tender, bilateral inguinal adenopathy	Present during primary infection
Charncroid	Tender papule, then painful, undermined purulent ulcer, single or multiple	Tender, regional, painful, suppurative nodes	None
Lympho-granuloma	Small, painless vesical or papule progresses to an ulcer	Painful, matted, large nodes, develop with fistula tracts	Present after genital lesion heals

management of patients with confirmed STI. Clinical characteristics of sexually transmitted genital ulcers are summarized in Table 1. Other causes that are not sexually transmitted such as Behcet's syndrome, drug reaction, erythema multiforme, Crohn's disease, lichen planus, amebiasis, trauma, and carcinoma should also be considered in the differential diagnosis. Empiric treatment for the most likely cause based on history and physical should be initiated as laboratory test results are pending. If ulcers do not respond to therapy or appear unusual, a biopsy should be performed.

HERPES SIMPLEX VIRUS

Diagnosis

Genital herpes infection is common, afflicting more than 50 million people in the USA. It is caused by HSV-2 in 85–90% of cases and HSV-1 in 10–15% of cases. HSV-1 is responsible for common cold sores but can be transmitted through oral secretions during oral-genital sex. Silent infection is common and may account for more than 75% of viral transmission *(10)*. Up to 80% of women with HSV-2 antibodies have no history of clinical infection *(11)*. The incubation period ranges from 1–26 days but is usually short, approximately 4 days. Nongenital infection of HSV-1 during childhood may be protective to some extent against subsequent genital HSV-2 infection in adults. When exposed to HSV-2, women with negative HSV-1 antibodies had a 32% risk of infection per year, whereas women with positive antibodies had a 10% risk of infection per year.

Primary infection manifests with painful ulcers of the genitalia or anus, and bilateral painful inguinal adenopathy. The initial presentation for HSV-1 and HSV-2 are the same though HSV-1 is expected to become the more common cause of first episode *(4)*. A group of vesicles on an erythematous base that does not follow a neural distribution is pathognomonic for herpes simplex *(12)*.

The initial infection is often associated with constitutional flu-like symptoms. Sacral radiculomyelopathy is a rare manifestation of primary infection that has a greater association with primary anal HSV. Genital lesions, especially urethral lesions, may cause transient urinary retention in women. Recurrent episodes are usually less severe, involving only ulceration of the genital or anal area. Severe disease and complications of herpes include pneumonitis, disseminated infection, hepatitis, meningitis and encephalitis. Asymptomatic shedding occurs more frequently with HSV-2 than HSV-1, even in patients with long-standing or clinically silent infection. Asymptomatic viral shedding is more likely during the 3–12 months following clinical presentation, thereby, perpetuating the risk of transmission *(4,12)*.

The diagnosis of genital herpes should not be made on clinical suspicion alone as the classic presentation of the ulcer occurs in only a small percentage of patients. Women especially may present with atypical lesions such as abrasions, fissures, or itching *(13)*. Viral culture with subtyping has been the gold standard of diagnosis of herpes infection. The viral subtype should be determined in every patient as it is important for prognosis and counseling. Women with HSV-2 have an average of four recurrences within the first year and women with HSV-1 have one recurrence in the first year. After the first year, HSV-1 rarely recurs while the rate of HSV-2 decreases but slowly *(14)*. Viral culture can generally isolate the virus in 5 days and is relatively inexpensive and highly specific. However, the sensitivity of viral culture ranges from 30 to 95% depending on the stage of the lesion and whether it is the primary infection or a recurrence. Viral load is highest when the lesion is vesicular and during primary infection. Therefore, viral culture has the highest sensitivity at these times and declines sharply as the lesion heals.

There are currently four FDA-approved glycoprotein G-based type-specific antibody assays: HerpeSelect™-1 enzyme-linked immunosorbent assay (ELISA) immunoglobulin G(IgG), HerpeSelect™-2 ELISA IgG, HerpeSelect™ 1 and 2 Immunoblot IgG (Focus Technology, Inc., Herndon,VA), and HSV-2 ELISA (Trinity Biotech USA, Berkeley Heights, NJ). These tests identify antibodies to HSV glycoproteins G-1 and G-2, which evoke a type-specific antibody response *(15)*. These tests may also be able to identify recently acquired versus established HSV infection based on antibody avidity *(16)*. Biokit HSV-2 (Biokit USA, Lexington, MA) and SureVue HSV-2, (Fisher Scientific, Pittsburgh, PA) are point-of-care tests that can provide results for HSV-2 antibodies from capillary blood or serum during a clinic visit *(2)*.

Treatment

Antiviral therapies approved for treatment include oral acyclovir, valacyclovir, and famciclovir. Recommended antiviral regimens are listed in Table 2. Topical antiviral medications are not effective. Recurrences can be treated with an episodic or suppressive approach. When used for episodic treatment, medication must be initiated during the prodrome or within 1 day of the onset of lesions. Daily suppressive therapy has been shown to prevent 80% of recurrences and is an option for patients who suffer

Table 2
Recommended Oral Treatment for Genital HSV

Agent	*First clinical episode*	*Episodic therapy*	*Suppressive therapy*
Acyclovir	400 mg tid for 7–10 days or 200 mg five times per day for 7–10 days	400 mg tid × 5days or 200 mg five times per day for 5 days or 800 mg bid for 5 days	400 mg bid
Famiciclovir	250 mg tid for 7–10 days	125 mg bid for 5 days	250 mg bid
Valacyclovir	1 g bid for 7–10 days	500 mg bid for 3–5 days or 1 g qd for 5 days	500 mg qd or 1 g qd

Adapted from Sexually Transmitted Diseases Guidelines 2002. *MMWR* 2002; 51(RR-6): 14.

from frequent recurrences. It has been shown to decrease the frequency and duration of recurrences as well as viral shedding and therefore reduction in the rate of transmission. The safety and efficacy of daily suppressive therapy has been well documented.

CHANCROID

Diagnosis

Chancroid, caused by *H. ducreyi*, is the most common STI worldwide. It affects men three times more often than women. The incubation period ranges from 1 to 21 days. It causes a painful, nonindurated ulcer on the penis or vulvovaginal area. The ulcer has a friable base covered with a gray or yellow purulent exudate and a shaggy border. It can spread laterally by apposition to inner thighs and buttocks, especially in women. It is associated with inguinal adenopathy that is typically unilateral and tender with tendency to be become suppurative and fistulize.

Haemophilus ducreyi is fastidious and difficult to culture. The special culture media is not widely available and sensitivity of culture remains less than 80%. Gram-stain of a specimen obtained from the undermined edge of the ulcer may be more helpful in identifying the short, fine, gram-negative streptobacilli, which are usually arranged in short, parallel chains. Recently, PCR assays have been shown to be a sensitive and specific means of detecting *H. ducreyi*. Although no PCR test is currently FDA approved, testing can be performed by commercial agencies. Approximately, 10% of persons who have chancroid are coinfected with *T. pallidum* or HSV (Ref:CDC). HIV and syphilis screening should be performed at the time of diagnosis and 3 months after treatment if initially negative.

Four criteria should be considered in formulating the diagnosis of chancroid: presence of one or more painful ulcers, presence of regional lymphadenopathy, a negative *T. pallidum* evaluation or negative serologies at least 7 days after the onset of symptoms, and negative HSP culture from the ulcer exudate *(4)*.

Treatment

Single-dose treatments consist of azithromycin 1 g orally or ceftriaxone 250 mg intramuscularly. Alternative regimens include ciprofloxacin 500 mg twice daily for 3 days or erythromycin base 500 mg by mouth three times daily for 7 days. However, antibiotic susceptibility varies geographically. Resistance has been reported to ciprofloxacin and erythromycin in some regions. Ciprofloxacin is contraindicated during pregnancy and lactation. Subjective improvement should be noted within 3 days and ulcers generally heal completely in 7–14 days. Healing may be slower in uncircumcised men with ulcers below the foreskin and in patients with HIV *(17)*. Patients should be re-examined in 5–7 days. Sexual partners should be examined and treated if sexual relations were held within 2 weeks prior to or during the eruption of the ulcer. Symptomatic relief of inguinal tenderness can be provided by needle aspiration or incision and drainage of the buboes.

SYPHILIS

Diagnosis

Syphilis is caused by a spirochete, *T. pallidum*. Incubation periods range between 10 and 90 days. It is spread through contact with infectious lesions or body fluids. It can also be acquired in utero and through blood transfusion. Primary syphilis is characterized by a single painless, indurated ulcer occurring at the site of inoculation that appears about 3 weeks after inoculation and persists for 4 to 6 weeks. The ulcer is typically found on the glans, corona, or perianal area on men and on the labial or anal area on women. It is often associated with bilateral, nontender inguinal or regional lymphadenopathy. As the ulcer and adenopathy are painless and heal without treatment, primary syphilis often goes unnoticed.

Latent syphilis is defined as seroreactivity with no clinical evidence of disease. Early latent syphilis is latent syphilis acquired within the past year. All other latent syphilis is either referred to as late latent syphilis or latent syphilis of unknown duration.

Secondary syphilis usually begins 4–10 weeks after the appearance of the ulcer but may present as long as 24 months following the initial infection. Secondary syphilis manifests with mucocutaneous, constitutional and parenchymal signs and symptoms. Frequent early manifestations consist of maculopapular rash which is commonly seen on the trunk and arms, and generalized nontender lymphadenopathy. After several days or weeks, a papular rash may accompany the primary rash. These papular lesions are associated with endarteritis and may therefore become necrotic and pustular. The distribution widens and commonly affects the palms and soles. In the intertriginous areas, these papules may enlarge and erode to produce condyloma lata that are particularly infectious. Less common manifestations of secondary syphilis include hepatitis and immune complex-induced glomerulonephritis.

Approximately, one-third of untreated patients will develop tertiary syphilis. It is very rare in industrialized countries, except for occasional cases reported in HIV patients. Syphilis is a systemic disease that can affect almost any organ or system especially the cardiovascular, skeletal and central nervous systems, and skin. Aortitis, meningitis, uveitis, optic neuritis, general paresis, tabe dorsalis, and gummas of the skin and skeleton are just some of the sequelae associated with tertiary syphilis.

Dark-field microscopy and direct fluorescent tests should be performed of specimens obtained from primary or secondary lesions. Dark-field microscopy is not widely

available, but DFA testing of a fixed smear from a lesion can be performed at many commercial laboratories. Nontreponemal serologic testing with rapid plasma regain (RPR) or Venereal Disease Research Laboratory (VRDL) is the most common method of screening suspected individuals. Sensitivity is 78 and 86% for RPR and VDRL, respectively, in primary syphilis, 100% for both in secondary syphilis and over 95% in tertiary syphilis *(18)*. The false-positive rate is approximately 1–2% and may be secondary to a large variety of causes *(19)*. Therefore, all positive tests should be confirmed with treponemal testing using *T. pallidum* particle agglutination (TP-PA) or florescent treponemal antibody absorbed (FTA-ABS). HIV can cause false-negative results by both treponemal and nontreponemal methods *(20,21)*. Positive treponemal antibody tests usually remain positive for life and do not correlate with disease activity. Nontreponemal antibody titers, RPR and VDRL, correlate with disease activity. These tests usually become negative 1 year after treatment. For following disease activity, the same test, either RPR or VRDL, should be performed at the same lab as the results are not interchangeable and may vary from laboratory to laboratory.

The US Preventive Services Task Force recommends that pregnant women and people who are at higher risk for syphilis infection receive screening tests for the disease *(22)*. People at higher risk for syphilis include men who have sex with men and engage in high-risk sexual behavior, commercial sex workers, persons who exchange sex for drugs, and those in adult correctional facilities. The CDC recommends that HIV testing should be considered in the initial evaluation of all patients with syphilitic infection and that screening for hepatitis B and C, gonorrhea, and chlamydial infection also should be considered. The presence of chancres increases the risk of HIV acquisition twofold to fivefold *(23,24)*.

Treatment

Benzthiazide penicillin G (2.4 million units intramuscularly as a single dose) remains the treatment of choice. Other parental preparations or oral penicillin are not acceptable substitutes. The Jarisch–Herxheimer reaction is a reaction consisting of headache, myalgia, fever, tachycardia, and increased respiratory rate that occur within the first 24 h after treatment with penicillin. Patients should be warned about the reaction, and it is usually managed with bed rest and nonsteroidal antiinflammatory agents. It may cause fetal distress and preterm labor in pregnant women.

If the patient has penicillin allergy, doxycycline 100 mg by mouth twice daily for 14 days is an alternative. For late latent syphilis, latent syphilis of unknown duration, or tertiary syphilis, benzthiazide penicillin injection should be repeated weekly for a total of three doses or doxycycline therapy extended for a total of 4 weeks. In pregnancy, doxycycline should not be used, and desensitization to penicillin is recommended if the patient has a penicillin allergy.

Teritary syphilis is treated with aqueous crystalline penicillin G, 3–4 million units IV every 4 h for 10–14 days; or penicillin G procaine, 2.4 million units IM once daily, plus probenecid, 500 mg orally four times daily, with both drugs given for 10–14 days. Probenecid cannot be used in patients with an allergy to sulfa. Patients should be followed with nontreponemal antibody titers at 6 and 12 months. Patients with neurosyphilis require repeat examination of CSF fluid 3–6 months following therapy and every 6 months afterward until normal results are achieved.

LYMPHOGRANULOMA VENEREUM

Diagnosis

Lymphogranuloma venereum is caused by *C. trachomatis* types L1, L2, and L3 and is extremely rare in the USA. It still persists in parts of Africa, Asia, South America, and the Caribbean *(25)*. The incubation period ranges from 3–30 days. The initial manifestation of infection is usually a single, painless ulcer on the penis, anus, or vulvovaginal area that goes unnoticed. Patients usually present with painful unilateral suppurative inguinal adenopathy and constitutional symptoms that occur 2–6 weeks after resolution of the ulcer. Women and homosexual men may present with proctocolitis and perirectal or deep iliac lymph-node enlargement if the primary lesion arises from the rectum or cervix. Significant tissue injury and scarring may occur, leading to labial fenestration, urethral destruction, anorectal fistulas, and elephantiasis of the penis, scrotum, or labia.

The diagnosis is mainly clinical, and cultures are positive in only 30–50% of cases. Compliment-fixation or indirect-fluorescence antibody titers can confirm diagnosis. A compliment fixation titer less than or equal to 64 is diagnostic of infection. Other causes of inguinal adenopathy should be excluded.

Treatment

Antibiotic therapy for 3 weeks is necessary, using either doxycycline 100 mg twice daily or erythromycin 500 mg four times daily. Doxycycline is contraindicated in pregnant and lactating women. Patients should be followed clinically until symptoms resolve. Sexual partners should be examined, tested for urethral or cervical infection, and treated if sexual relations were held within 30 days of the onset of symptoms.

Buboes may require aspiration or incision and drainage to prevent femoral or inguinal ulcerations. Azithromycin, 1 g, by mouth weekly for 3 weeks may be a potential alternative for treatment, but data are still lacking.

URETHRITIS, EPIDIDYMITIS, AND CERVICITIS

Diagnosis of urethritis in men is based on any one of the following three criteria: mucopurulent or purulent penile discharge, gram stain of urethral secretions demonstrating less than five WBC per oil immersion field, or positive leukocyte esterase on first-void urine (or first-void urine specimen demonstrating less than 10 WBC per oil immersion field). Gonococcal urethritis can be diagnosed by gram stain, as a positive gram stain is 99% specific and 95% sensitive. However, a negative gram stain in the setting of urethritis does not rule out gonococcus *(4)*.

Epididymitis is defined as inflammation of the epididymis and may be infectious (bacterial, viral, fungal, or parasitic) or noninfectious (trauma, autoimmune, amiodarone-induced, and so on). The differential diagnosis of testicular torsion must also be considered as this is a surgical emergency that could result in testicular loss if not treated immediately. In young men, the most common cause of infectious epididymitis is STI. In heterosexual men less than 35 years old, the most common causes are *N. gonorrhoeae* and *C. trachomatis*. In MSM, *E. coli* and *Haemophilus influenzae* are the most common *(26)*.

Patients usually present with scrotal swelling and pain. Palpation may reveal a prominent and tender epididymis or a large tense erythematous mass which is painful

and warm to touch. If it also involves the testis, it is known as epididymo-orchitis. Laboratory findings that are consistent with a diagnosis of epididymitis include pyuria, bacteriuria, a positive urine culture, and leukocytosis. However, normal urinalysis and white count do not rule it out. The CDC recommends that the evaluation of men for epididymitis should include one of the following: ∘ Gram stain of urethral secretions demonstrating less than five WBC per oil immersion field (Gonococcal infection is established by documenting the presence of WBC containing intracellular Gram-negative diplococci on urethral Gram stain) or positive leukocyte esterase test or pyuria (>10 WBC per high power field) on first-void urine. Culture, nucleic acid hybridization tests, and nucleic acid amplification tests previously discussed for gonorrhea and chlamydia should be performed. For patients at risk, consideration should be given for further STD testing. Treatment includes supportive therapy of bed rest, scrotal elevation, antiinflammatory agents and Ceftriaxone 250 mg IM in a single-dose PLUS Doxycycline 100 mg orally twice a day for 10 days. Of epididymitis is most likely caused by enteric organisms or for patients allergic to cephalosporins and/or tetracyclines: ofloxacin 300 mg orally twice a day for 10 days or levofloxacin 500 mg orally once daily for 10 days. In an acute setting, testicular torsion should be an important consideration in the differential diagnosis.

Cervicitis is characterized by two major diagnostics signs: purulent or mucopurulent endocervical exudate and/or sustained endocervical bleeding easily provoked by swabbing the cervical os. Indeed, some women with cervicitis may have no other symptoms than bleeding post-coitally or anormal vaginal discharge.

The following sections will address the most common causes of cervicitis, urethritis, and epididymitis in patients with STD exposure.

CHLAMYDIA TRACHOMATIS

Diagnosis

This is the most common bacterial STD in the USA and the most common worldwide. In the USA, it is most prevalent in sexually active adolescents and young adults. Virulent serotypes include D, E, F, G, H, I, J, and K. The incubation period ranges from 3–14 days.

The majority of both men and women are asymptomatic. Approximately 50% of men experience lower urinary tract symptoms attributed to urethritis, epididymitis, or prostatitis, and may notice clear or white urethral discharge. *C. trachomatis* is the most common cause of epididymitis in young men. Approximately 75% of women are asymptomatic and 40% with untreated infection will develop PID *(27)*. Scarring of the fallopian tubes from chlamydial infection puts patients at risk for recurrent PID with vaginal flora, ectoptic pregnancy, pelvic pain, and infertility *(28)*.

Chlamydia may also be transmitted to newborns during vaginal birth through exposure of the mother's infected cervix. Neonates may contract ocular, oropharyngeal, respiratory, urogenital, or rectal infection.

Selective screening has been shown to reduce the incidence of PID *(29)*. Women should be screened annually until age 25 or if risk factors such as a new sexual partner are present. In women, screening may be accomplished by (i) a nucleic acid amplification test (NAAT) performed on an endocervical swab specimen if a pelvic examination is acceptable; otherwise, a NAAT is performed on urine, (ii) an unamplified nucleic acid hybridization test, an enzyme immunoassay, or DFA test performed on

an endocervical swab specimen, or (iii) culture performed on an endocervical swab specimen. In men, the options remain the same but intraurethral samples must be used.

Treatment

Azithromycin 1 g by mouth as a single dose or doxycycline 100 mg twice daily for 7 days are primary treatments and equally effective. Alternative therapies include erythromycin base 500 mg four times daily, erythromycin ethylsuccinate 800 mg four times daily, ofloxacin 300 mg twice daily, or levofloxacin 500 mg daily for 7 days. Doxycycline, erythromycin estolate, and ofloxacin are contraindicated during pregnancy. Erythromycin base, erythromycin ethylsuccinate, and azithromycin are safe during pregnancy. Another alternative in pregnant women includes amoxicillin 500 mg three times per day for 7 days. Partners should be examined, tested, and treated. Patients should refrain from sexual intercourse until both they and their partner's treatment is completed or 7 days after single-dose therapy. Reculture for cure is not needed for patients treated with doxycycline or a quinolone antibiotic. It is recommended 3 weeks after treatment with erythromycin as cure rates are lower with this regimen, in pregnant women, or if the patient has persistent symptoms. However, patients with chlamydia are at high risk for reinfection and should be rescreened 3–4 months after treatment.

GONORRHEA

Diagnosis

Gonorrhea is caused by a gram-negative diplococcus, *N. gonorrhoeae*. The incubation period ranges from 3–14 days. Risk of infection after one exposure is 10% in men and 40% in women. Men will usually experience lower urinary tract symptoms attributed to urethritis, epididymitis, proctitis, or prostatitis, with associated mucopurulent urethral discharge. Women may have symptoms of vaginal and pelvic discomfort, dysuria, or abnormal vaginal discharge but are most often asymptomatic. Both symptomatic and asymptomatic infections can lead to PID and its subsequent complications. Therefore, screening in all sexually active adolescents and women up to the age of 25 should be performed yearly. In addition, any women with risk factors such as a new sexual partner or multiple sexual partners should be screened. Manifestations of gonococcal dissemination are rare today and include arthritis, dermatitis, meningitis, and endocarditis.

The CDC recommends screening by culture on an endocervical swab specimen in women or an intraurethral swab in men *(30)*. A positive gram stain of a male urethral swab is highly specific (99%) and sensitive (95%). Presence of WBC and diplococci are confirmatory; however, a negative gram stain does not rule out GC. Gram stain of secretions from pharynx, cervix, or rectum are insufficient for the diagnosis of GC and are not recommended *(4)*. Culture and sensitivity are important to monitor antibiotic susceptibility and resistance. Culture may be performed on urethra exudates if present. If transport and storage conditions are not conducive to maintaining the viability of *N. gonorrhoeae*, a NAAT or nucleic acid hybridization test can be performed. If it is not possible to obtain an intraurethral or endocervical specimen, NAAT may be performed on urine. Urine NAATs for *N. gonorrhoeae* have been shown to be less sensitive than endocervical and intraurethral swabs in asympotomatic men *(31)*.

Treatment

The most highly recommended treatment for gonorrhea is ceftriaxone 125 mg intramuscularly as a single dose. It produces high, sustained blood levels that result in cure in over 99% of uncomplicated cases at all anatomic sites. An oral alternative is a single oral dose of cefixime 400 mg. Cefixime is no longer available in tablet formulation in the USA but can be obtained as a suspension. Alternative single-dose parenteral agents for urogenital and anorectal gonorrhea include ceftizoxime 500 mg, cefoxitin 2 g with probenecid 1 g orally, or cefotaxime 500 mg. For patients with penicillin or cephalosporin allergies, a single intramuscular dose of spectinomycin 2 g is a recommended alternative but not available in the USA. A single 2-g dose of azithromycin is effective in uncomplicated infections but is not recommended by the CDC because of increasing resistance. It may be an option for treatment of uncomplicated infections in patients with documented severe allergic reactions to penicillins or cephalosporins.

Over the past decade, there has been the rapid emergence of quinolone-resistant *N. gonorrhoeae* (QRNG). Areas where QRNG are most prevalent include parts of Asia, the Pacific, Hawaii, and California *(32)*. Initially, quinolones were not adviced as primary therapy in these states or in patients who have had recent sexual encounters with people from these areas. However, quinolone resistance in other areas in the USA has rapidly increased. In April 2007, the CDC announced that it no longer recommends quinolones for the treatment of gonococcal infection in any population.

Quinolones are contraindicated during pregnancy. Spectinomycin 2 g IM can be used during pregnancy or in patients allergic to quinolones and cephalosporins. Spectinomycin is not as effective for pharyngeal infection.

Patients infected with gonorrhea are often coinfected with *C. trachomatis*. It has been recommended that patients undergo simultaneous dual treatment because the cost of treatment is less than that of chlamydial testing. All patients diagnosed with gonorrhea should be treated with for possible coinfection with *C. trachomatis* with a single dose of azithromycin 1 g or with doxycycline 100 mg twice a day for 7 days unless chlamydial infection has been ruled out.

If greater than 60 days has gone, the most recent sexual partner should be evaluated and treated. Sexual activity should be avoided until both partners complete treatment and are symptom free. Persons with persistent symptoms or recurrence shortly after treatment should be reevaluated by culture for *N. gonorrhoeae*, and positive isolates should undergo antimicrobial-susceptibility testing. Clinicians and laboratories should report treatment failures or resistant gonococcal isolates to CDC at 404-639-8373 through state and local public health authorities *(33)*.

TRICHOMONIASIS

Diagnosis

Trichomoniasis is one of the most common sexually transmitted diseases, with approximately 174 million new cases reported world wide each year and more than 8 million new cases reported yearly in North America *(34)*. There is an increased incidence in developing countries and in women who have had multiple sexual partners. It is caused by the flagellated protozoan *Trichomonas vaginalis*, which can inhabit the vagina, urethra, Bartholian glands, Skene's glands, and prostate. It cannot infect the rectum or mouth. The human is its only known host. The incubation period ranges from 4–28 days.

It is typically asymptomatic in men but may produce short-lived symptoms of urethral discharge, dysuria, and urinary urgency. Fifty percent of women are asymptomatic. Clinical manifestations in women include the sudden onset of a frothy white or green, foul smelling vaginal discharge, pruritis, and erythema. Other symptoms include dyspareunia, suprapubic discomfort, and urinary urgency. It has been associated with premature labor in pregnant women and with increased risk of HIV transmission *(35,36)*.

Clinical examination may reveal a frothy discharge and the characteristic "strawberry vulva" or "strawberry cervix." However, clinical assessment alone is not specific enough for diagnosis. Typically, the vaginal discharge has an elevated pH. The motile protozoa, which are one to four times the size of polymorphonuclear cells, can also be seen on vaginal wet-mount smear or microscopic examination of urine (preferably voiding bottle #1). Microscopic inspection of vaginal secretions has only a 60–70% sensitivity *(4)*. In men, the diagnosis is made with urethral culture or microscopic examination of urine (preferably voiding bottle #1.) Standard culture, transport culture kits, enzyme immunoassay, nucleic acid amplification, and immunofluorescence techniques are also available for confirmatory testing.

Treatment

Infected individuals and their sexual partners should be treated to prevent recurrence of infection. A single 2-g dose of metronidazole is effective in most cases and can be used in the second trimester of pregnancy. Metronidazole therapy is associated with a 90–95% cure rate, while tinidazole 2-g single dose is associated with 86–100% cure rate *(4)*. For nonpregnant treatment failures, a longer course of metronidazole, 500 mg twice daily for 7 days, is recommended. The dosing regimens appear equally effective; however, side effects, especially gastrointestinal side effects, are more common with the high-dose single therapy. Patients must abstain from alcohol consumption during therapy. Repeat testing at 5–7 days and 30 days should be performed if symptoms fail to resolve and treatment failure is suspected and a course of metronidazole 500 mg twice a day for 7 days should be repeated or 2 g once a day for 3–5 days may be tried. Metronidazole gel for intravaginal application is available, however, it is less than 50 % effective as oral treatment.

OVERVIEW OF OTHER VAGINITIDES

Ureaplasma urealyticum, Mycoplasma hominis, and *Mycoplasma genitalium* are considered commensal organisms of the genital tract in both men and women. It is estimated that at least 60% of sexually active women may harbor Ureaplasma in their genital tracts. These organisms however, have been implicated in cases of chronic prostatitis in men, urgency-frequency symptoms in women *(37)*, and in up to 40% of non-gonococcal urethritis cases *(38)*. Currently, the initial recommended therapy is doxycycline 100 mg twice daily for 2 weeks or a single dose of azythromycin, 1 g po which can be repeated in 10–14 days. Other alternatives include arithromyocine 500 mg four times daily or ofloxacin 300 mg twice daily for 10–14 days. Sexual partners should be evaluated and treated accordingly.

BV is caused by the overgrowth of a *Gardnerella vaginalis*, anaerobic organisms, Mycoplasma, and/or the inhibition of normal vaginal flora. The cause for disruption of the microflora may be due to douching, abnormal uterine bleeding, contraceptive use, or increased number of sexual partners. Vaginal secretions should be examined using

10% potassium hydroxide (10% KOH) to observe a fishy odor secondary to the release of amines. These specimens should also be examined under the microscope. Three out of the four following factors must be met to confirm the diagnosis of BV: (i) Thin, white vaginal discharge that covers the vagina, (ii) vaginal pH > 4.5, (iii) clue cells, and (4) positive width test (KOH). There are commercially available DNA probes and card tests that can be used for office diagnosis. The recommended primary therapy includes metronidazole 500 mg twice daily for 7 days, clindamycin cream 2% intravaginally at bedtime for 7 days, or metronidazole gel 0.75% intravaginally at bedtime for 5 days *(39,40)*.

Vaginitis caused by *Candida albicans* is the most common type seen in the clinical setting; however, there are other species of *Candida* that may cause similar presentations. Characteristically, thick, cheesy vaginal discharge is usually associated with vulvar irritation and itching. However, patients may also experience vaginal discomfort, burning, dyspareunia, and external dysuria. The diagnosis can be confirmed in a woman with signs and symptoms by findings of yeast or psuedohyphae on a wet preparation slide or a gram stain of the vaginal discharge. The yeast and pseudohyphae are better seen after the application of 10% KOH. Over-the-counter antifungal vaginal creams, tablets, or suppositories of the topical azole class are generally effective and require 1–7 days of treatment. The treatment agents include butoconazole, clotrimazole, miconazole, and terconazole. An alternative to vaginal creams that is both effective and economical is fluconazole, 150 mg as a single oral dose. Recurrent infections should prompt evaluation to rule out diabetes mellitus and HIV.

HUMAN PAPILLOMA VIRUS

Diagnosis

Genital warts (*Condylomata acuminata*) are caused by HPV. HPV is a DNA containing virus, which is spread by direct skin to skin contact. Over 100 types of HPV exist and over 30 types can infect the genital area. Risk factors for acquiring HPV include multiple sexual partners, early age on onset of sexual intercourse, and having a sexual partner with HPV. Most infections are subclinical and asymptomatic. It has been shown that 60% of a group of female college students followed by PAP smear every 6 months for 3 years were infected with HPV at some point. The median duration of HPV infection was 8 months, with only 9% remaining infected after 2 years *(41)*.

Types 6 and 11 of HPV are most often responsible for visible external genital warts. Patients may be infected with more than one type of HPV. Genital warts may appear anywhere on the external genitalia. It has been suggested that inoculation occurs at the site of genital micro-trauma *(42)*. HPV has can also been found on the cervix, vagina, urethra, anus, and on mucous membranes such as the conjunctiva, mouth, and nasal passages.

Types 6 and 11 HPV are low risk for conversion to invasive carcinoma of the external genitalia. Some other types present in the anogenital region, notably types 16, 18, 31, 33, 35, 39, 45, and 51, have been associated with cervical dysplasia and neoplasm in women and squamous intraepithelial neoplasia in men *(43–45)*. Over 99% of cervical cancers and 84% of anal cancers are associated with HPV, most commonly HPV 16 and 18 *(46,47)*. Because HPV progresses rapidly in HIV-infected women, cervical cancer is considered one of the AIDS-defining illnesses. Smoking may increase the risk of dysplastic progression and malignancy in both men and women.

In women, HPV may be associated with nonspecific symptoms, such as vulvodynia or pruritis. Malodorous vaginal discharge may also be a presenting sign, and the high rate of co-infection with other STDs observed in this setting may be a contributing factor.

The diagnosis is usually made through the visualization or palpation of nontender papillomatous genital lesions. Aceto-whitening with 3–5% acetic acid placed on a towel and wrapped around the genitals may show subclinical, flat condylomas appearing as whitish areas. Using this method, it was shown that 50–77% steady male partners of women with HPV infection and/or cervical neoplasia had subclinical HPV infection *(48)*. Conversely, female partners of men with genital warts have a high incidence of HPV infection *(49)*. The benefit of evaluating and treating asymptomatic sexual partners of women with genital warts or abnormal PAP smears remains unclear. Routine androscopy is not recommended. Biopsies of genital warts are not routinely needed but should be undertaken in all instances of atypical, pigmented, indurated, fixed, or ulcerated warts. In addition, biopsy should be performed if the lesions persist or worsen after treatment and in immunocompromised patients.

Treatment

The CDC currently recommends that patients with genital warts be informed that HPV and recurrence is common among sexual active persons, the incubation period can be long and variable, and duration of infection and methods of prevention are not definitively known. The choice of therapy for genital warts depends on several factors including wart size, number and location, and patient and physician preference. As genital warts spontaneously resolve with time, observation remains an option. Therapy can be patient applied or provider applied. Patient-applied therapies are less expensive and may be more effective than provider-applied therapy *(50,51)*.

Recommended treatment choices for patient-applied therapy include podofilox 0.5% solution or gel and imiquimod 5% cream *(52)*. Podofilox solution should be applied every 12 h for 3 days, then off for 4 days with the option to repeat the treatment cycle four times. The total volume of solution used should not exceed 0.5 ml per day and the total wart area should not be greater than 10 cm^2. It may be helpful to demonstrate the first application in the office. Imiquimod cream should be applied three times per week at bedtime for up to 16 weeks. The area should be thoroughly washed 6–10 h after application. Imiquimod should not be used on vaginal lesions as it has been reported to cause chronic ulceration. Neither medication should be used in pregnancy.

Options for provider-applied therapy include cryotherapy with liquid nitrogen, electrosurgery, laser therapy, podophyllin resin 20–25%, trichloroacetic acid (TCA) or bichloroacateic acid (BCA) 80–90%, or surgical excision. Surgical excision may be accomplished by electrocautery or sharply with a tangential incision. Bleeding can generally be controlled with electrocautery or silver nitrate application. Surgical therapies appear to be equally effective with regards to clearance rates *(53)*. The advantages of surgical excision are that large warts or large areas can be addressed at one time. Carbon dioxide laser therapy is an alternative option for treatment.

Podophyllin 10–25% in compound tincture of benzoin is applied once and washed thoroughly 1–4 h after treatment. Treatment may be repeated weekly as needed. Podophyllin is contraindicated during pregnancy. TCA and BCA should be carefully applied with a cotton tip applicator only to the warts at 1–2 week intervals. Patients will complain of a burning sensation that should resolve in 2–5 min. Unreacted acid

should be removed with baking soda or talc. TCA and BCA are not preferable for keratinized or large warts. TCA is not absorbed and may be used during pregnancy.

Women with genital warts or a history of exposure should seek prompt gynecologic evaluation of the vagina and cervix. In the past, extensive vulvar lesions were treated with 5-FU cream, but it was reported to cause ulceration and acquired adenosis, and its use is no longer recommended.

The presence of genital warts is not an indication for HPV testing, a change or frequency of PAP tests or cervical colposcopy. HPV testing is not indicated for partners of persons with genital warts *(4)*. All patients, however, should be reminded of the importance of regularly scheduled gynecological exams and annual Pap tests.

Large or extensive lesions surrounding the meatus may herald the presence of urethral or bladder condyloma, warranting cystourethroscopy. Urethral or bladder lesions should be cytoscopically excised. Intraurethral 5% FU cream used twice weekly may be useful. However, it is limited by the great amount of inflammation produced *(54)*.

Topical application of viable Bacille Calmette-Guerin (BCG) has also shown promising preliminary results, but larger studies are needed to fully evaluate its safety and efficacy *(55)*.

HPV Vaccine

Two virus-like particle HPV vaccines have been developed. Gardasil (Merck & Co., Inc.) is a quadrivalent vaccine against HPV types 6, 11, 16, and 18 and was approved by the FDA in June 2006 for the prevention of HPV-associated conditions such as cervical cancer, cervical cancer precursors, and anogenital warts. Cervarix (GlaxoSmithKline) is a bivalent vaccine against HPV types 16 and 18 and has been filed for FDA approval. The surrogate marker for cervical cancer used in the clinical trials was the combined incidence of HPV 16- and 18-related grade 2 or 3 cervical intraepithelial neoplasia (CIN 2/3) or adenocarcinoma in situ (AIS) *(56)*. In study participants with no evidence of previous infection with the HPV 6,11,16, or 18 who completed the three immunization series with no protocol violations, the quadrivalent HPV vaccine showed 100% efficacy for preventing vaccine type-related CIN 2/3 and AIS, external genital warts, and vulval/vaginal intraepithelial neoplasia *(57,58,59)*. The vaccine also had high efficacy for the prevention of vaccine type HPV-related persistent infection *(60)*. Participants infected with one or more vaccine HPV types before vaccination were protected against disease caused by the remaining vaccine HPV types *(60)*. No evidence exists that the vaccine protects against disease caused by non-vaccine HPV types or for disease caused by vaccine types for which participants were PCR positive at baseline *(56)*.

The bivalent vaccine also showed 100% efficacy in preventing HPV16- or HPV18-related CIN *(61)*. A subset of subjects in the phase II study of the quadrivalent vaccine have completed 5 years of follow-up *(62)*. At 5 years, the combined incidence of HPV 6-,11-,16-, and 18-related persistent infection or disease was reduced in vaccine recipients by 96%, and no vaccine recipient developed HPV 6-,11-,16-, or 18-related precancerous cervical dysplasia or genital warts.

As the quadrivalent vaccine is the only one available at the time of this publication, the following recommendation can only be applied to it. The ACIP (CDC's Advisory Committee on Immunization Practices) has recommended routine vaccination of females aged 11–12 years with three doses of quadrivalent HPV vaccine, but it

can be started in girls as young as 9 years of age *(59)*. The three vaccination series is given at 0, 2, and 6 months. It is preferable that the vaccine be administered prior to sexual activity or known exposure to HPV for optimal benefit. "Catch-up" vaccination is recommended for women aged 13–26 years who have not been previously vaccinated or who have not completed the three vaccine series. Vaccination provides less protection to those who have already been infected with one or more of the four vaccine HPV types. However, vaccination is still recommended as these will still be protected against the other vaccine subtypes. In opposition to the CDC's guidelines, the American Cancer Society does not recommend universal vaccination among women aged 19–26 years because of a probable reduction in efficacy as the number of lifetime sexual partners rise *(63)*.

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6 Bacterial Cystitis

Acute and Chronic

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Summary

Urinary tract infection is one of the most common health problems affecting patients of all ages. It is the most common nosocomial bacterial infection in the elderly. Women are especially prone to urinary tract infections (UTIs). Although prostatitis syndrome accounts for 25% of male office visits for genitourinary tract infections, only 5% are attributed to a bacterial cause. Acute cystitis or pyelonephritis in adult patients should be considered uncomplicated if there are no known functional or anatomic abnormalities of the genitourinary tact. Most of these infections are caused by *Escherichia coli*. Acute uncomplicated cystitis can be effectively treated with a 3-day course of trimethoprim/sulfametho oxazole (TMZ/SMZ). For acute uncomplicated pyelonephritis, a 10- to 14-day regimen is recommended. Sexually transmitted diseases including those caused by *Chlamydia, Mycoplasma hominis*, and *Ureaplasma urealyticum* should be considered potential culprits in sexually active patients.

Key Words: Bacterial cystitis; urinary tract infection; prostatitis; pyelonephritis; sexually transmitted disease; catheter-related infection.

Contents

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INTRODUCTION

Urinary tract infections (UTIs) are the most common nosocomial infections. They account for more than 7 million physician visits and over 1 million hospital admissions in the USA each year *(1,2)*. They are the most common bacterial infection in the elderly and the most frequent source of bacteremia *(3,4)*. Catheter-associated UTI is the most common nosocomial infection, accounting for less than 1 million cases in hospitals and nursing homes *(5)*.

DEFINITIONS

The term uncomplicated UTI refers to the invasion of structurally and functionally normal urinary tract by a nonresident infectious organism. Complicated UTI refers to the occurrence of infection in most men and in patients with abnormal structural and/or abnormal functional urinary tract (Table 1). It also refers to UTI acquired by or associated with urinary tract instrumentation or catheterization.

PREVALENCE AND RISK FACTORS

In 1995, the estimate for the USA puts the direct cost of community-acquired UTI at $659 million and indirect costs, through lost productivity, at $936 million *(5–8)*. The incidence ratio of UTIs in middle-aged women to men is 30:1; however, during later

Table 1
Functional and Structural Abnormalities of the Genitourinary Tract

1. Functional abnormalities
   - Vesicoureteral reflux
   - Neurogenic bladder
2. Obstruction
   - Congenital abnormalities
   - Pelviureteric obstruction
   - Ureteric and urethral strictures
   - Urolithiasis
   - Bladder[25] diverticuli
   - Tumors
3. Foreign bodies
   - Indwelling catheters
4. Other
   - Diabetes mellitus
   - Renal failure
   - Urinary diversions
   - Urinary instrumentation

decades of life, the ratio of infection in women to men with bacteriuria progressively decreases *(9)*. Since these estimates were made, the number of cases and the cost of management have increased.

Approximately, 20% of all UTIs occur in men. Men older than 85 had nearly twice as many emergency room visits for UTI as did men younger than 85. (In men, UTI manifested as orchitis is more common than cystitis and pyelonephritis.) Overall medical expenditure for men with UTI in 2000 was estimated to be $1.028 billion *(10)*. In women, several trends have been observed recently. While fewer younger women are being hospitalized for UTI, there has been an increase of inpatient care for UTI among elderly women. There is also an increased trend in prescribing fluoroquinolones as first-line therapy, which is associated with increased cost. In 2000, the estimated medical expenditure for UTI in women was $2.57 billion *(11)*. Women are especially susceptible to cystitis for reasons that are poorly understood. One factor may be that a woman's urethra is short, allowing bacteria quick access to the bladder. Also, a woman's urethral opening is near sources of bacteria from the anus and vagina. For many women, sexual intercourse seems to trigger an infection, although the reasons for this linkage are unclear *(10,12)*. Estimates suggest that about a third of women will have at least one episode of UTI requiring antibiotic therapy by the time they are 24 years old and over a lifetime half will have at least one UTI *(5–7)*. Hormonally induced changes in the vaginal flora associated with the menopause are responsible for its higher prevalence in older women *(13)*.

PATHOGENESIS OF UTI

The infection spreads to the urinary tract either through an ascending route of fecal flora, from the fecal reservoir through the urethra into the bladder, particularly in patients with intermittent or indwelling catheters; hematogenous dissemination, secondary to *Staphylococcus aureus* bacteremia; or by direct extension from adjacent organs through the lymphatic system, as in the case of retroperitoneal abscesses or severe bowel obstruction. In female, colonization of the mucosa of the vaginal introitus is an essential step in the pathogenesis of UTI

Some people are more likely to get UTIs than others because of host factors or urothelial mucosa adherence to the mucopolysaccharide lining *(14)*. Any abnormality of the urinary tract that interferes with the drainage of urine (e.g., kidney stones or an enlarged prostate) sets the stage for an infection, as well as foreign bodies in the bladder such as catheters (Table 1). Diabetes and other immune compromised patients are at higher risk for UTI and its complications. Sexual intercourse *(12)* and women's use of a diaphragm *(15)* have also been linked to an increased risk of cystitis. Pregnancy does not increase the risk of cystitis; however, it increases the risk of pyelonephritis, if UTI occurs.

URINARY PATHOGENS

Escherichia coli is the most common infecting organism in patients with uncomplicated UTIs *(16)*. It causes 85% of community-acquired infections and approximately 50% of nosocomial infections. Other gram-negative microorganisms causing UTIs include *Proteus* sp., *Klebsiella* sp., *Citrobacter* sp., *Enterobacter* sp., and *Pseudomonas*

sp. Gram-positive pathogens such as *Enterococcus faecalis, Staphylococcus saprophyticus*, and group B streptococci can also infect the urinary tract. Anaerobic microorganisms are frequently encountered in suppurative infection of the genitourinary tract (e.g., periurethral abscess and Fournier's gangrene).

SIGNS AND SYMPTOMS

Cystitis may be asymptomatic. However, some patients report incontinence and/or a general lack of well-being *(17)* Cystitis clinically manifests as irritative voiding symptoms that include frequency, dysuria, urgency, suprapubic or lower abdominal pain, and incontinence. In men, urinary retention should be ruled out, as it is frequently associated with cystitis and possible prostatitis. The manifestations of UTI in elderly may include confusion, lethargy, anorexia, and incontinence.

DIAGNOSIS

Physical examination, including pelvic exam, should be carried out in women with lower urinary tract symptoms to exclude gynecological, neurological or colorectal disorders. Physicians should also maintain a high index of suspicion for underlying sexually transmitted disease. Up to 50% of women presenting to an emergency department for symptoms of cystitis were found to have positive sexually transmitted disease (STD) cultures *(18)*.

Urine samples are collected for urinalysis in a sterile container through urethral catheterization, especially in women, or by midstream-voided urine after the genital area is washed to avoid contamination. The sample is then tested for bacteriuria, pyuria, and hematuria. Indirect dipstick tests are informative but are less sensitive than microscopic examination of the urine. About one-third of the women who have acute symptoms of cystitis have either sterile urine or some other cause for the symptom *(19)*. Many diseases of the urinary tract produce significant pyuria without bacteriuria. These include stag horn calculi, tuberculosis, and infections caused by Chlamydia and Mycoplasma spp. Microscopic hematuria is found in 40–60% of cystitis cases *(20)*. Associated gross hematuria should be evaluated further by imaging studies. Cystoscopy is indicated in those patients who are more than 50 years old or have other risk factors for concomitant diseases such as nephrolithiasis or transitional cell carcinoma (e.g., smoking).

While empiric therapies are acceptable for uncomplicated cystitis (Table 2), culture and sensitivity testing should be performed in all other cases. It is important to bear in mind that a large percentage of women with lower urinary tract symptoms (LUTS) attributed to cystitis have been found to have STDs. Additional cultures for Neisseria gonorrhea, Chlamydia, *Mycoplasma hominis*, and *Ureaplasma urealyticum* should be considered for women with recurrent lower urinary tract symptoms. Noninfectious causes of LUTS must also be considered. These include overactive bladder, painful bladder syndrome, interstitial cystitis, diabetic cystopathy, and other neurological disorders, as well medication effects.

Radiological studies are unnecessary for the routine evaluation of patients with cystitis; however, they may be indicated to find the cause of complicated cases, where UTIs are associated with urinary calculi, ureteral strictures, ureteral reflux, urinary tract tumors, and urinary tract diversions.

Table 2
UTI in Adults

1. Uncomplicated
   - Acute cystitis in female
   - Acute pyelonephritis in young healthy female
2. Complicated
   - Acute cystitis in male
   - Acute prostatitis
   - Chronic prostatitis
   - Acute pyelonephritis in man
   - UTI with pregnancy
   - UTI with gross hematuria
   - UTI associated with nephrolithes
   - UTI associated with neurogenic bladder
   - UTI in diabetic or immunocompromised patient
   - Recurrent UTI (>3 episodes per year)

- Plain radiograph of the abdomen for the detection of radiopaque calculi or abnormal renal contour.
- Intravenous pyelogram for radiographic images of the bladder, kidneys, and ureters. An opaque dye visible on radiographic film is injected into the vein and a series of radiographs are taken. The films demonstrate the contour of the collecting system, which may reveal filling defects or obstruction.
- Voiding cystourethrogram for the evaluation of neurogenic bladder and urethral diverticulum and to exclude or define the extent of vesicoureteral reflux.
- Renal ultrasonography, through interpretaton of echo patterns generated by sound waves one can detect the presence of hydronephrosis, tumors, pyonephrosis, calculi, or abscess.
- Computed tomography (CT), a more sensitive means of defining renal parenchyma especially when used with intravenous contrast material. CT urograms have replaced intravenous pyelograms in the evaluation of the urinary tract and kidneys, particularly in the work up of hematuria. Spiral CT scan without contrast is the most sensitive means of detecting calculi within the urinary collecting system and is standard of care in the evaluation of acute flank pain.
- Magnetic resonance may be indicated in patients who require further evaluation for renal neoplasm, in whom IV contrast is contraindicated. It may also be necessary as the most sensitive modality for the detection of urethral diverticulum.

The urethra and the bladder can be inspected quickly and safely by the use of cystoscopy with a local anesthetic in an office setting.

Differential Diagnosis

When evaluating patients with LUTS, it is important to consider gynecological and colorectal diagnoses as well. STD in either sex, as mentioned earlier, may present as LUTS with or without fever. Female patients especially those presenting with severe symptoms and pain should be screened for pregnancy, as complications such as ectopic pregnancy or abortion should be ruled out. Chronic appendicitis and sigmoid diverticulitis may be confused with UTI or prostatitis. We have encountered several

patients referred for evaluation of persistent or recurrent UTI or prostatitis, in whom diverticulitis (and even rarer, chronic appendicitis) was proven to be the cause of their symptoms.

MANAGEMENT

For general management of cystitis, the patient is advised to drink plenty of water, which helps cleanse the urinary tract of bacteria. Cranberry juice and vitamin C (ascorbic acid) supplements inhibit the growth of some bacteria by acidifying the urine. Avoiding coffee, alcohol, and spicy foods may also be useful. Bladder analgesia may help diminish suprapubic discomfort and dysuria, when prescribed together with antibiotics.

Antibiotic selection is based on several criteria (Table 3). The sensitivity test is especially useful for the treatment of recurrent (culture proven) UTI.

Acute Cystitis

Patients who have symptoms of frequency, urgency, pyuria on microscopic examination, and no known functional or anatomic abnormality of the genitourinary tract may be presumed to have acute uncomplicated cystitis. Empirical therapy with a 3-day regimen of trimethoprim/sulfamethoxazole (TMP/SMZ) or a fluoroquinolone (FQs) without pretreatment culture and sensitivity testing is usually effective. Infectious Diseases Society of America guidelines state that uncomplicated UTI should be treated empirically with TMP/SMZ, unless community resistance among uropathogens exceeds 10–20%. FQs are cost drivers in the health care expenditure of community UTI *(21)*. They are less costly, however, in the setting of *E. coli* resistance exceeding 22% *(22)*. Some patients may require 7-day regimens, especially with elderly or with renal impairment. Nitrofurantoin should be avoided, however, in older patients because of increased susceptibility in this population for adverse effects *(23)*. Generally, for most female patients, a 3-day course seems warranted, as 3-day therapy demonstrates similar efficacy when compared with 7-day therapy and with lower side effects and cost *(24)*. Single-dose therapy usually results in lower rates of cure and more frequent recurrences.

Table 3
Factors Influencing the Selection of Antimicrobial Agents in Treating UTIs

1. Patient
   - History of drug allergy
   - Medical history (renal impairment and liver impairment)
   - Presence of urological abnormalities
2. Drug
   - Safety profile
   - Spectrum of activity
   - Route of administration
   - Costs
3. Organism
   - Gram's stain
   - Special culture & sensitivity

Recurrent Cystitis

The most common cause of recurrent UTI in women is reinfection that may occur with varying intervals as well as varying causative organisms. Reinfection in women does not require extensive urologic evaluation. Recurrent episodes of uncomplicated cystitis can be managed through several strategies. Behavioral therapy includes increasing fluid intake, urinating as soon as the need is felt as well as immediately after intercourse, and changing the method of contraception (for users of a diaphragm or spermicide) as spermicidal jelly containing nonoxynol-9 that decrease vaginal lactobacillus colonization and increasing bacterial adherence. Long-term antimicrobial prophylaxis *(25)*, postcoital prophylaxes with a single-dose antibiotic *(26)*, or short-course (1- or 2-day) antibiotics for each symptomatic episode is recommended. For postmenopausal women, the use of vaginal estrogen cream may prove an effective preventive measure *(13)*. Patients with bacterial persistence should be evaluated thoroughly to exclude potential structural or functional abnormalities.

For postmenopausal women, the use of vaginal estrogen cream may prove to be an effective measure *(20)*. Estrogen replacement therapy promotes a predominant Doderlein vaginal flora and enhances urethral mucosal health. Alterations in vaginal flora increase UTI susceptibility. Indeed, a higher incidence of UTI has been observed in women, following antibiotic therapy for other causes *(5)*.

Probiotics are of increasing interest for use in UTI prevention. Lactobacillus vaginal suppositories were shown to decrease the rate of UTI recurrence in one small pilot study. Women with history of recurrent UTI in previous 2 years were instructed to insert a suppository every other day. They were followed for 1 year *(27)*.

Prostatitis

Prostate infections are more challenging to cure because of the altered microenvironment of the inflamed tissue, which may affect antibiotic efficacy. For this reason, men with acute bacterial prostatitis often need long-term treatment (at least 30 days) with a carefully selected antibiotic. Severely ill patients need hospitalization and parenteral antimicrobial agents, such as an aminoglycoside–penicillin combination, until culture and susceptibilities provide guidance for alternative and specific antibiotic regimens. In men with urinary retention, a urethral or suprapubic catheter is necessary. Suprapubic catheterization is preferable to decrease the risk of prostatic abscesses. Mild and moderate cases respond well to fluoroquinolones or TMP/SMZ, both of which have a cure rate of 60–90% *(28)*. Chronic bacterial prostatitis may manifest as episodes of recurrent bacteriuria with the same organism between asymptomatic periods. Episodic treatment may be prescribed using the agents mentioned above and in selected patients may be self-prescribed as needed. Daily suppressive therapy should be considered in men with frequent cystitis if other causes are excluded and the culpable organism is localized to the prostate, using the Meares–Stamey technique *(29)*.

Two separate chapters in this book present an extensive discussion about bacterial and nonbacterial prostatitis.

Sexually Transmitted Infections

Special cultures are needed to diagnose these infections. Antibiotic therapy should be prescribed accordingly. Longer treatment with tetracycline, doxycycline, or any drug appropriate for the treatment of *Mycoplasma hominis* and *Ureaplasma urealyticum* is

recommended *(30)*. Sexual partner must be treated simultaneously. A separate chapter containing a comprehensive review of STI is included in this book.

Catheter-Related Infections

In 1998, it was estimated that 12% of hospital patients and 4% of patients living in the community have a urinary catheter at any given time *(31)*.

Catheterization for more than 2 weeks is usually associated with bacteriuria. Prophylactic antimicrobial therapy for cystitis during short-term, indwelling, urethral catheterization is not recommended. Symptomatic UTI in elderly should be treated. Careful consideration is required of antimicrobial choice and meticulous monitoring of the drug levels in this patient population as the elderly patient is more susceptible to harmful side effects of many antimicrobial agents. Short-term antimicrobial therapy (5–7 days) is indicated only in symptomatic episodes. In patients requiring long-term urinary catheterization, suprapubic catheter placement should be considered. In men, suprapubic catheterization is associated with decreased risk of meatal erosion or prostatitis. In the short term, suprapubic catheterization may be associated with a decreased risk of bacteruria or UTI. Unfortunately, this difference does not exist in long-term catheterization *(32)*.

Funguria is a common finding in catheterized patients. While most patients are asymptomatic, interventions should include change in catheter, elimination of unnecessary antimicrobials, and glycemic control. Although amphotericin B may be used for bladder irrigations, it is less effective and more expensive than oral fluconazole therapy, though the latter is a concern in patients with hepatic vulnerability.

Removal of an indwelling catheter should be prompt; whenever possible, intermittent self-catheterization should be used in patients with transient or long-term urinary retention.

Asymptomatic Bacteriuria

Bacteriuria denotes the presence of bacteria in the urine, which may be symptomatic or asymptomatic. The incidence of bacteruira increases with age. The prevalence is greater in women. Bacteruria is significantly greater among diabetic women; however, diabetes does not appear to increase the prevalence of bacteruia among men *(5)*. Treatment of asymptomatic bacteriuria is indicated in pregnant women and in those requiring urologic surgery *(33)*. Preoperative treatment reduces postoperative complications, including bacteremia *(34)*.

Cystitis with Pregnancy

Although the prevalence of bacteriuria identified by screening is no higher in pregnant females than nonpregnant females, the presence of asymptomatic bacteriuria in a pregnant woman should be treated promptly *(35)*. The gravid uterus causes physiological alterations that increase the risk of pyelonephritis. Pyelonephritis has been associated with infant prematurity, low birth weight, perinatal mortality, and high blood pressure *(36)*. The recommended regimen of treatment is a 7-day treatment of ampicillin or nitrofurantoin.

There appears to be an increased risk of asymptomatic bacteruria during pregnancy among women with history of childhood UTI. The rate of risk is associated with the absence of renal scarring, 27%, or the presence of renal scarring, 47% *(5)*.

Urinary Tract Infection with Renal Failure

When creatinine clearance is significantly impaired, antibiotic dosage should be decreased as the renal blood flow is decreased and the perfusion of antimicrobial agents into the renal tissue and urine is impaired. Ampicillin, TMP/SMZ, and fluoroquinolones are all effective in the treatment of UTI in uremic patients *(37,38)*. Nitrofurantoin and tetracyclines are contraindicated for the treatment of UTIs in uremic patients.

Prophylaxis

Antimicrobial prophylaxis is recommended to ensure the sterility of urine for those who appear susceptible to developing infections. These include immunocompromised patients, patients with heart disease, people with a prosthetic heart valve, and patients who are scheduled for a procedure, for example, cystoscopy. Oral or vaginal estrogen administration prophylactically to postmenopausal women also reduces the incidence of cystitis *(33,38)*.

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7 Anorectal Pain

What is the Cause and How Should it be Managed?

Jill C. Genua, MD, and Dana R. Sands, MD

Summary

Anorectal pain is distressing for the patient and challenging for the physician. The vague and inconsistent use of terms such as proctalgia fugax, levator ani syndrome, spastic pelvic floor, coccygodynia, chronic idiopathic anorectal pain, and pelvic floor dyssynergia make it difficult to identify a cause and an effective therapy. Many conditions, some of which may be potentially fatal, must be excluded before the diagnosis of chronic idiopathic anorectal pain, including conditions of proctalgia fugax and levator spasm, can be made. Therapy for anorectal pain targets muscle spasm though no one therapy has proven ideal. An organized algorithm and a tactful patient approach are required for the management of anorectal pain.

Key Words: Anorectal pain; proctalgia fugax; levator ani syndrome; levator spasm; chronic idiopathic anal pain; functional anorectal disorders; pudendal neuralgia; coccygodynia.

Contents

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INTRODUCTION

Anorectal pain is distressing for the patient and challenging for the physician. Many terms have inconsistently been used to describe conditions of anorectal pain such as proctalgia fugax, levator ani syndrome, spastic pelvic floor, coccygodynia, chronic idiopathic anorectal pain, and pelvic floor dyssynergia. These vaguely defined terms make it challenging to identify a cause and an effective therapy. Each patient with the complaint of anorectal pain must be thoroughly evaluated to exclude many conditions which may present with anorectal pain. Once excluding those causes, some of which are potentially fatal, the diagnosis of chronic idiopathic anorectal pain can be applied; this term includes the conditions of proctalgia fugax and levator spasm. Therapy for anorectal pain targets muscle spasm; many therapies have been tried but none has emerged as ideal. An organized algorithm and a tactful patient approach are required for the management of anorectal pain.

The relief of pain is one of the most rewarding situations in the relationship between physician and patient. Conversely, refractory pain due to an unclear cause is a frustrating challenge. Unfortunately, the latter scenario often surrounds the clinical entity of anorectal pain.

The terms proctalgia fugax, levator spasm, spastic pelvic floor syndrome, coccygodynia, pelvic floor dyssynergia, idiopathic pelvic pain, and anorectal neuralgia have all been used to describe conditions of anorectal pain. The definitions are often vague or imprecise, and the terms have been used interchangeably. These inconsistencies permeate the literature, including studies of the treatment of anorectal pain, thus making it difficult for the physician to categorize and effectively relieve anorectal pain. In addition, patients have often been evaluated by multiple physicians and may have undergone unsuccessful procedures in attempts to treat this pain. Because of these factors, the management of anorectal pain requires an organized, thorough, and patient approach.

DEFINING AND CLASSIFYING ANORECTAL PAIN

In 1841, Hall described a "peculiar and severe pain of the rectum which comes on in paroxysms, generally during the first sleep." The condition was described again in the later half of the nineteenth century *(1)*. Thaysen is credited for the term "proctalgia fugax" to describe the paroxysmal rectal pain *(2)*. Proctalgia was once believed to be a disease of tense, perfectionist men *(3–5)*.

In 1999, the consensus statement of an international panel (Rome II) established criteria for two anorectal pain disorders: levator ani syndrome and proctalgia fugax *(6)*. The disorders are considered functional disorders of the anus and rectum, meaning they have no structural, infectious, or biochemical basis *(5,7)*. According to the Rome II diagnostic criteria, the levator ani syndrome is chronic or recurrent rectal pain or aching which lasts 20 min or longer; the symptoms must have been present for at least 12 weeks of the preceding 1 year *(6)*. The pain of levator ani syndrome is classically described as a vague discomfort high in the rectum with or without rectal pressure; patients sometimes report the feeling of sitting on a ball or other intrarectal object *(6,8,9)*. The discomfort is believed to be caused by spasm of the levator ani muscle which is composed of the ileococcygeus, the pubococcygeus, and the puborectalis *(9)*. The levator muscle is sometimes felt as a tight band on physical examination of

patients with this syndrome; palpation of the muscle may reproduce or precipitate the pain *(10)*.

The diagnostic criteria for proctalgia fugax are recurrent episodes (lasting seconds to minutes) of sudden and severe anorectal pain; the pain disappears completely between attacks *(6)*. Patients typically report the sudden onset of intense, sharp, stabbing, or cramping pain at any time of day, but frequently the pain will cause them to wake up at night *(8)*. The episodes are relatively infrequent (approximately five episodes in a 12-month period). The interaction of nerves, vessels, and striated muscle that produces the paroxysmal pain of proctalgia fugax is poorly understood and the mechanism may not be the same in all patients *(5)*. The idea of proctalgia as an "unusual variant of the irritable bowel syndrome" was suggested, but later evidence refutes this theory *(11,12)*. The finding that calcium channel blockers stop the attacks in some patients suggest that pain is caused by vasospasm *(13)*. Two families with hereditary proctalgia fugax have been reported in the literature *(14,15)*. The affected members of these families exhibit internal anal sphincter hypertrophy and hypertonia suggesting myopathy as a cause of proctalgia. There is one report of episodes of proctalgia correlating with paroxysmal high amplitude, high-frequency myoelectrical activity of the anal sphincter *(16)*. A study of 18 patients with proctalgia fugax matched with 18 control patients demonstrated that patients with proctalgia fugax have normal anorectal function and morphology in the resting state, but a rise in anal resting tone and abnormal anal muscle motility during an attack *(17)*. However, another study of 18 patients with chronic idiopathic anal pain revealed no distinguishing findings on anorectal physiology, intraanal ultrasound, or biopsies of the sphincter muscles *(18)*.

ETIOLOGY OF ANORECTAL PAIN

The majority of patients with anal pain and irritation present with the complaint of hemorrhoids; many will have another cause of their pain and some will have idiopathic anal pain *(8)*. To effectively manage anal pain, a classification of the various etiologies is presented in Table 1.

There are various intraluminal causes of anorectal pain such as proctitis, solitary rectal ulcer, and rectal cancer; these specific conditions and their treatments are beyond the scope of this chapter. Extraluminal causes of anorectal pain include pelvic masses, prostate pathology, endometriosis, pelvic inflammatory disease, coccygodynia, and presacral tumors. Coccygodynia is sometimes classified as chronic idiopathic anal pain but is really a distinct pain that can be evoked with pressure or manipulation of the coccyx. Sacral tumors or tumors of sacral nerve structures, trauma, avascular necrosis, and referred pain from prolapsed lumbar disks are all reported causes of coccygodynia *(19–26)*.

Presacral tumors are associated with pain with 40% of benign lesions and 60–80% of malignant ones *(27)*. Presacral tumors are clinically rare and diagnostically challenging; an index of suspicion in all patients complaining of anorectal pain should be maintained. Among 34 patients with retrorectal tumors treated at a single institution, 71% reported sacrococcygeal pain; others reported rectal fullness and pressure with defecation *(28)*. In a review of patients referred to the colorectal departments of two institutions with misdiagnosed retrorectal cysts, the masses were correctly diagnosed by physical examination and CT scan in all cases once the diagnosis was suspected *(29)*. Therefore, including presacral tumors in the differential diagnosis of anorectal

Table 1
Etiology of Anorectal Pain

Intraluminal
Proctitis
Solitary rectal ulcer syndrome
Fecal impaction or foreign body
Rectal cancer
Extraluminal
Pelvic masses
Endometriosis
Pelvic inflammatory disease
Prostate pathology
Coccygodynia
Presacral tumors
Anal
Hemorrhoids
Fissure
Abscess/fistula
Pruritus ani
Cutaneous infections/dermatitis
Anal cancer
Neurologic
Spinal
Pudendal nerve entrapment
Pelvic floor disorders/ pelvic floor dyssynergia
Postoperative
Low anterior resection
Hysterectomy
Anorectal surgery
Idiopathic
Levator ani syndrome
Proctalgia fugax

pain along with adequate examination and investigational studies will identify this rare but important condition.

Anal pathology including hemorrhoids, fissures, abscess, fistula in ano, pruritus ani, cutaneous infections/dermatitis, and anal carcinoma can each present with the symptom of anal pain. These causes are identified by thorough examination, and treatment should be directed to each specific cause.

Neurologic causes of anorectal pain include spinal causes (trauma, disk herniation, etc.) and pudendal nerve entrapment. Despite limited descriptions in the literature, neuralgia of the pudendal nerves because of entrapment is the cause of anorectal pain in some patients. The pudendal nerve, which arises from S2, S3, and S4 of the sacral plexus, is potentially trapped in two areas of its anatomic course: between the sacrotuberous and sacrospinous ligament and in the pudendal canal of Alcock (a thickening of the obturator internus fascia) *(30)*. Bicyclists are at increased risk due to repeated trauma of the perineum and chronic inflammation and fibrosis in the pudendal canal and the sacrospinous/sacrotuberous ligaments. The pain of pudendal

nerve entrapment is described as positional in nature (worse when sitting, relieved when sitting on lavatory seat or standing) *(31)*. Tenderness of the pudendal nerve and reproduction of the pain on palpation of a trigger point have been consistently described *(32)*. The diagnosis can be confirmed and treated by performing nerve blocks under CT or ultrasound guidance *(33,34)*. A small number of patients have had documented pain relief after surgical decompression *(30,35)*.

Anorectal pain may be a complaint of patients with pelvic floor disorders. In a study of 302 consecutive female patients who presented to a tertiary urogynecology clinic with pelvic organ prolapse and incontinence, 25% also had an anorectal pain disorder *(36)*. However, these patients are likely reporting the pressure and discomfort of prolapse; they do not necessarily have distinct anorectal pain. Therefore, although patients may interpret and report their condition as anorectal pain, they should be isolated diagnostically and therapeutically from patients with other etiologies of anorectal pain. Similarly, pelvic floor dyssynergia may present with the complaint of anorectal pain, but this entity should be distinguished. According to the Rome II criteria, pelvic floor dyssynergia is diagnosed by functional constipation, paradoxical contraction or failure to relax the pelvic floor musculature during defecation, and incomplete evacuation *(6)*. As with all pelvic floor disorders, the diagnostic evaluation and therapy should be directed according to the underlying disorder, and the associated pain should be distinguished from idiopathic anorectal pain disorders.

A significant number of patients will have postoperative anorectal pain. The most obvious group is those patients who have undergone anorectal surgery such as hemorrhoidectomy. However, prolonged periods of anorectal pain are reported by some patients following pelvic procedures such as hysterectomy and low anterior colon resections. The pain is likely secondary to inflammation and reactive spasm of the muscles of the pelvic floor; however, pain may represent a complication specific to the procedure which was performed (i.e., postoperative abscess). In the absence of postoperative complications related to the procedure performed, the pain will usually subside and resolve with time.

After excluding intraluminal and extraluminal causes, anal pathology, neurologic conditions, pelvic floor disorders, and postoperative anorectal pain, the disorder of idiopathic anorectal pain can be applied. Idiopathic anorectal pain includes the conditions of levator ani syndrome and proctalgia fugax. These diagnoses should not be applied until the above causes have been ruled out.

EVALUATION OF ANORECTAL PAIN

The evaluation of anorectal pain begins with a thorough history. The history should focus on the character of the pain, relation to defecation and position, and its distribution. Questions regarding dyspareunia, pain with ejaculation, dysuria, constipation, and straining with defecation should be included. The presence of new masses, bleeding, drainage/discharge, and change in bowel habits should be noted. General past medical history should elicit comorbidities (i.e., diabetes) and history of neurologic issues, prostatitis, irritable bowel syndrome, inflammatory bowel disease, and psychiatric disorders. Compliance with routine screening guidelines such as those for colorectal cancer, prostate cancer, and gynecologic conditions should be enforced and documented. The past surgical history should identify a history of surgery in the anorectal area, obstetric history including anal sphincter injury, and prior spinal surgery.

The importance of a complete anorectal examination of a patient complaining of anorectal pain cannot be stressed enough. The patient should be examined in the prone jack-knife position if possible. Inspection alone will sometimes reveal a diagnosis responsible for the patient's pain. Palpation should include digital rectal examination; this may not be possible if an obvious fissure is present upon inspection. In some cases, a trigger point of pain along the pudendal nerve or levator spasm is palpable. The coccyx and sacrum should be palpated to exclude coccygodynia or pilonidal disease as the source of the reported anorectal pain. Anoscopy should follow digital rectal examination.

Endoscopy is essential to rule out intraluminal causes of anorectal pain. A flexible sigmoidoscopy may be sufficient; however, standard guidelines for colonoscopy should be followed. If history, physical examination, and endoscopy do not diagnose an obvious source of pain, CT scan of the pelvis should be performed. Prior to the diagnosis of functional anal pain, endorectal ultrasound and pelvic MRI may be useful at this stage of evaluation.

In the absence of concomitant pelvic floor dysfunction, physiologic testing is generally not helpful in the evaluation of anorectal pain. If the patient reports evacuation dysfunction, constipation, or incontinence, then anal manometry, cinedefecogram, EMG, and pudendal nerve testing should be performed as necessary. The anorectal pain should be considered a component of these disorders rather than a primary pain disorder.

MANAGEMENT OF ANORECTAL PAIN

Figure 1 outlines a management algorithm of patients with anorectal pain. After a thorough history, a physical examination, and diagnostic studies, the structural, inflammatory, infectious, and mechanical causes of anorectal pain are identified and appropriately managed. The treatment of the remaining patients (without a demonstrated abnormality or obvious source of the pain) remains elusive and challenging. The physician must be extremely patient and sensitive.

Once potentially fatal causes of anorectal pain are ruled out, management of anorectal pain begins with reassurance and conservative therapies. A bowel regimen including fiber supplementation should be stressed to minimize constipation and straining, which may contribute to the patient's discomfort. Perineal strengthening exercises are also a conservative recommendation to help maximize the efficiency of the pelvic floor in attempt to minimize pain. Because anorectal pain is believed to be related to muscle spasm, a popular conservative recommendation is soaking in a warm water bath or sitz baths. Hot water baths have been demonstrated to significantly reduce resting anal canal pressures on anal manometry; this finding may explain why patients with anorectal pain benefit from sitz baths *(37)*.

When reassurance and conservative measures do not bring enough relief, the first line of medication may be suggested. This includes the use of mild analgesics and NSAIDS, muscle relaxants, and topical local anesthetics. At this stage of management, operative transanal digital massage of the puborectalis muscle with or without an injection of steroid to the muscle has been described *(38)*.

Several therapies for anorectal pain have been reported, but none has emerged as preferred or optimal treatment. Ger et al. assessed the evaluation and treatment of chronic intractable rectal pain in sixty consecutive patients *(39)*. The study consisted

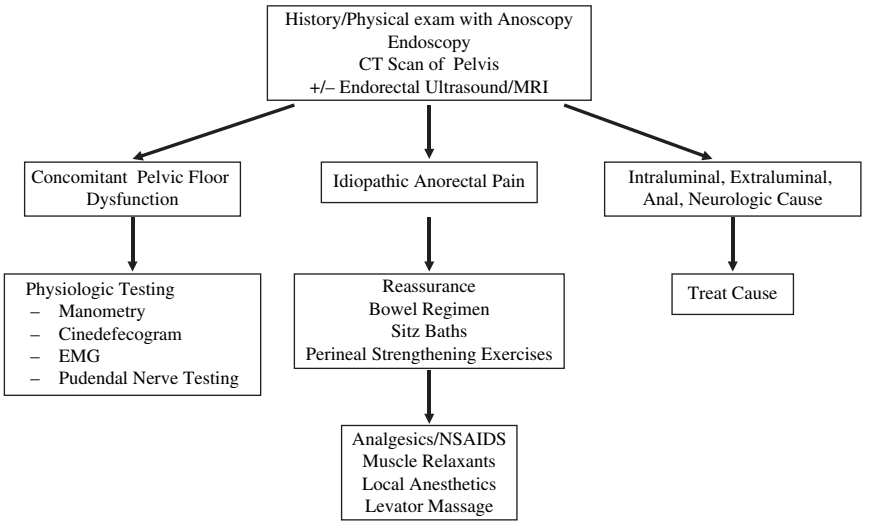

Fig. 1. Management of anorectal pain.

of 23 males and 37 females with mean age of 69 (range 29–87) years. The patients had symptoms of anorectal pain for an average of 4.5 years, had all failed conservative management, and extensive evaluation had ruled out organic causes of the pain. Three therapies were used to treat these patients: electrogalvanic stimulation (EGS) (29 patients), biofeedback (14 patients), and steroid caudal block (11 patients). Overall success of pain relief was found in 47% of the patients. Thirty-eight percent of patients after EGS, 43% of patients following biofeedback, and 18% of patients following steroid caudal block experienced what they described as good or excellent pain relief. More than half of the patients were refractory to all three therapeutic options. The authors concluded that the treatment of chronic intractable rectal pain is best described as a "frustrating endeavor."

Biofeedback is a process whereby the patient observes information regarding body functions in order to be trained to modify the function. It has been used for various functional gastrointestinal disorders and disorders of the pelvic floor and has been employed for the treatment of anorectal pain *(40–42)*. In one study of 16 patients with levator ani syndrome, there was significant reduction in the patient-reported use of NSAIDS and in pain ratings following biofeedback therapy *(41)*. Gilliland et al. performed a retrospective review of 86 patients with rectal pain who were treated with at least one session of biofeedback therapy *(40)*. They concluded that biofeedback therapy is effective in alleviating rectal pain. However, the success depends on the patients' compliance with attending sessions and completing the entire course of therapy as determined by the therapist. All studies of biofeedback therapy for anorectal pain are uncontrolled, but many demonstrate promising results *(42)*. Biofeedback is not first-line therapy; however, for those patients who are motivated, it may benefit them without risk of harm or worsening of the symptoms.

Other second-line therapies for anorectal pain include linearly polarized near-infrared irradiation *(43)*, steroid caudal block *(39)*, and EGS *(44–49)*. EGS involves three 1-h treatments over 6 days, whereby a probe is placed in the rectum to deliver high-voltage,

low-frequency oscillating electric current *(38)*. The current causes fasciculation and fatigue of the levator muscle.

Second-line therapies such as biofeedback and EGS require specialized equipment and patient motivation. Other second-line therapies include the use of various medications. Diltiazem (80 mg twice a day) has been tried *(13)*. Reports of oral clonidine (beginning at 150 μg twice daily with a tapering dosages over 1 week) have reportedly relieved proctalgia fugax *(50)*. Topical 0.2–0.3% nitroglycerin had a successful response in a small number of reported patient *(51,18)*. Because of the success of treatments which target muscle spasm, Botox® injection into the intersphincteric groove has been used with significant improvement in some patients *(18)*. The only randomized, double-blind, placebo-controlled trial for proctalgia fugax investigated inhaled salbutamol *(52)*. In this study of 18 patients, salbutamol significantly shortened the attacks of rectal pain with an unclear mechanism.

Despite the many options for management of anorectal pain, and even in situations where the physician follows an organized algorithm, the fact remains that pain is a complicated condition to treat which often involves multiple variables. For example, there is often a significant psychological component to pain which either initiates the pain or develops as a result of the distress of unrelieved pain. The physician should be tactful and sensitive to this aspect of anorectal pain and suggest psychological support and evaluation as needed. A formal pain management program is also an extremely valuable resource. Trained pain specialists can offer additional therapies such as differential and diagnostic pain blocks *(53)*. Acupuncture, in addition to being derived from thousands of years of experience, is yet another therapy available as a definitive therapy for those patients who have failed other options or as adjunctive therapy for those who have responded *(54)*.

CONCLUSION

Anorectal pain is distressing for the patient and challenging for the physician. Many terms have inconsistently been used to describe conditions of anorectal pain such as proctalgia fugax, levator ani syndrome, spastic pelvic floor, coccygodynia, chronic idiopathic anorectal pain, and pelvic floor dyssynergia. These vaguely defined terms make it challenging to identify a cause and an effective therapy. Each patient with the complaint of anorectal pain must be thoroughly evaluated to exclude many conditions which may present with anorectal pain. Once excluding those causes, some of which are potentially fatal, the diagnosis of chronic idiopathic anorectal pain can be applied; this term includes the conditions of proctalgia fugax and levator spasm. Therapy for anorectal pain targets muscle spasm; many therapies have been tried but none has emerged as ideal. An organized algorithm and a tactful, patient approach is required for the management of anorectal pain.

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8 Gastroenterological Causes of Pelvic Pain

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SUMMARY

Chronic abdominal pain accounts for 10% of gynecological consultations and over 30% of diagnostic laparoscopies. There are numerous causes of chronic pelvic pain, and it is important to consider non-gynecologic causes such as gastroenterological, urological, and neurological causes. The most common gastroenterological cause of chronic abdominal and pelvic pain is irritable bowel syndrome (IBS), but other gastrointestinal conditions such as diverticular disease of the colon, inflammatory bowel disease, endometriosis, colorectal cancer, hernias, proctalgia fugax, levator ani syndrome, and chronic appendicitis must be considered in the differential diagnosis. When evaluating a patient with IBS and chronic pelvic pain, it is extremely important to establish a relation of trust and respect with the patient, to include a social history, explore the possibility of emotional, physical, or sexual abuse because these are factors that are often ignored by health care providers and have a significant impact in the disease process, symptoms, and clinical outcome. The gastrointestinal system performs complex functions that require the proper function of the intrinsic nervous system (enteric nervous system), central nervous system, neuroendocrine and immune systems. The neuroendocrine system plays an important role in the regulation of intestinal motility, secretions, and visceral sensation. Between 90 and 95% of the serotonin in the human body is found within the gastrointestinal system, particularly within the epithelial layer. There are numerous abnormalities that have been described in IBS including abnormal enterochromaffin cell numbers, serotonin content, tryptophan hydroxylase levels, 5-hydroxyindoleacedic acid levels, serum serotonin levels, and expression of the serotonin-selective reuptake transporter. Therefore, serotonin agonists and antagonist alter sensory input and have a significant effect in gut function including secretion and motility *(1,2)*. The concept of "visceral hyperalgesia"

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was proposed by Ritchie in 1973 *(3)*, this concept has helped us better understand the pathophysiology and symptoms of IBS, and conceptually, it serves as the basis for some pharmacological treatments; however, this knowledge has not translated into better diagnostic modalities.

Key Words: Irritable bowel syndrome; chronic pelvic pain; functional gastrointestinal disorders; diarrhea; constipation; abuse; antispasmatic agents; bulking agents; $5HT_3$; $5HT_4$; serotonin; alosetron; tegaserod.

Contents

INTRODUCTION

Chronic pelvic pain is a major health problem that affects 10–20% of men and women. It significantly impairs the quality of life of these patients, can lead to invasive and expensive investigations, and in many patients the etiology of the pelvic pain can not be found even after extensive investigations including surgical procedures. Pelvic pain represents 10% of all patient visits to a gynecologist, is responsible for approximately 40% of laparoscopies and 10–15% of hysterectomies performed by gynecologists. These patients have four times more non-gynecologic operations and are five times more likely to have a hysterectomy *(4–6)*. Women with chronic pelvic pain use three times more medications of any type. Chronic pelvic pain is characterized by constant or intermittent pain in the lower abdomen confined to the anatomic pelvis that lasts for at least 6 months; potential causes of chronic abdominal pain include gastrointestinal, urological, and gynecological disorders. It is believed that the reason why pelvic pain can be caused by such a variety of disorders is that the function of the intestinal system, lower urinary tract, gynecologic, and sexual function are all inter-related. An extensive description of the anatomy and physiology of the pelvic floor is beyond the scope of this chapter, but it is important to remember that all of these functions are involuntary and coordinated by nerve connections or reflexes. The pelvic organs are innervated by both sympathetic and parasympathetic autonomic nerves, as well as somatic sensory nerves. The visceral afferent nerves travel by both sympathetic and parasympathetic fibers and as the somatic nerves; they enter the spinal cord primarily through the dorsal horns, then the stimuli are carried to the pain centers of the brain by spinothalamic and spinoreticular neurons. Within the pelvis, the inferior hypogastric plexus innervates the bladder, urethra, rectum, internal anal sphincter, and genital and reproductive organs. The inferior hypogastric plexus receives neural projections from spinal roots T10-L1 through the superior hypogastric plexus and from

S2-4 through branches from the sacral plexus. The external anal sphincter and the levator muscles are controlled by somatic fibers through the sacral nerves. The posterior perineal muscles and the skin of the perineal, perianal and the labia are innervated by nerves that originate from S4 and S5. The inferior hypogastric plexus is considered the major integrative center; it is believed that because of these common neural pathways there can be "cross-sensitization" amongst the different pelvic organs. Therefore, acute or chronic irritation of one pelvic organ can lead to abnormal function, sensitization, and even neurogenic-mediated inflammation in another organ. Another element that is very important to understand in regards to the perception of visceral pain is that acute injury or inflammation, such as in an infectious process, can sensitize the visceral receptors in the abdomen and pelvis and lead to hyperalgesia or allodynia. This may explain the post-infectious irritable bowel syndrome and may play a role in post-pelvic inflammatory disease pain. Irritable bowel syndrome (IBS) is frequently associated with fibromyalgia and interstitial cystitis; these associations likely occur because the regulation of abdominal and pelvic pain is not determined only by afferent fibers, but there is also an efferent pathway; and the changes in the descending modulatory system have an effect in neural impulses regardless of its source.

The commonest gastrointestinal disorder causing chronic pelvic pain is irritable bowel syndrome. Half the women with chronic pelvic pain also have symptoms related to IBS, genitourinary symptoms, or both. Importantly, between 40 and 60% of patients with IBS also experience urinary urgency and 40–50% of patients with interstitial cystitis also have IBS *(7,8)*. The enteric nervous system has almost as many neurons as the spinal cord, however, its main function is in the regulation of the normal intestinal function, the sensory fibers of the enteric nervous system do not contribute to conscious sensation because they do not project to the central nervous system.

IRRITABLE BOWEL SYNDROME

When patients have symptoms that cannot be explained on the basis of an identifiable structural abnormality, the disorder is considered a "functional problem". A functional disorder is frequently attributed to physiological, psychological, and sociocultural factors that influence the patients' perception of symptoms. IBS is considered a "functional disorder" of the gastrointestinal tract; it is the most common disease managed by primary care physicians and by gastroenterologists. Unfortunately, physicians and patients frequently equate "functional diseases" with psychological derangements, "stress disorders," or "disorders of living," and some physicians even stigmatize these patients *(9)*. In the past 20 years, there has been improved understanding of the irritable bowel syndrome as a "functional gastrointestinal disorder (FGID)"; and the description of the "gut–brain axis" has allowed us to better evaluate IBS in the context of genetics, environmental, psychological, and physiologic factors. The abnormalities in IBS include alterations in visceral sensitivity, intestinal motility, and function of the central and enteric nervous systems and the neuroendocrine system.

For years, it was difficult to interpret the magnitude of the problem and to establish treatment guidelines because the diagnostic criteria were not standardized. In the 12th International Congress of Gastroenterology in Portugal in 1984, a group of experts decided to create guidelines for the study and treatment of IBS. These guidelines were presented in 1988 at the "International Congress of Gastroenterology" in Rome, Italy (Roma 1988), and in 1989, these recommendations were published *(10)*. The

group continued to work from 1988 through 1994 and develop criteria to classify functional disorders of the gastrointestinal system; in 1994, these criteria were published and the document became known as "Rome I" *(11)*. The group was expanded and continued deliberations, and in 1999, the "Rome II" document was published in a special supplement of the journal *Gut (12)* and in 2000 in a book published by Degnon Associates *(13)*.

Functional disorders of the gastrointestinal system are very important because they are common and have a significant impact on patients and society. The extraordinary work of the group continued, and a formal organization was created, and in 2002, the "Rome Board" met in London England and formalized "The Multinational Working Teams for Diagnosis of Functional GI Disorders"; this is an international group composed of 87 experts from 18 countries divided in 14 committees. The aim of this group was to define and categorize the FGIDs such as irritable bowel syndrome. This led to the "Rome III criteria" that were presented during the American Gastroenterological Association meeting in Los Angeles in 2006, and published as a whole issue in *Gastroenterology*, April 2006, Vol 130, No 5.

Table 1
Rome III Diagnostic Criteria for Irritable Bowel Syndrome

- Esophageal (category A)
- Gastroduodenal (category B)
- Bowel (category C)
  - Irritable bowel syndrome
  - Functional bloating
  - Functional constipation
  - Functional diarrhea
  - Unspecified functional bowel disorder
- Functional abdominal pain syndrome (category D)
- Biliary (category E)
- Anorectal (category F)

Adapted from Ref. *(13)*.

Table 2
C1 Irritable Bowel Syndrome[a]

Diagnostic Criteria
Recurrent abdominal pain or discomfort[b] at least 3 days per month in the last 3 months associated with two or more of the following: 1. Improvement with defecation 2. Onset associated with a change in frequency of stool 3. Onset associated with a change in form (appearance) of stool

[a] Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.
[b] Discomfort means an uncomfortable sensation not described as pain.
Adapted from Ref. *(13)*.

Table 3
Subtyping IBS by Predominant Stool Pattern

1. IBS with constipation (IBS-C)—hard or lumpy stools[a] $\geq$ 25% and loose (mushy) or watery[b] stools $<$ 25% of bowel movements[c]
2. IBS with diarrhea (IBS-D)—loose (mushy) or watery stools[b] $\geq$ 25% and hard or lumpy stools[a] stools $<$ 25% of bowel movements[c]
3. Mixed IBS (IBS-M)—hard or lumpy stools[a] $\geq$ 25% and loose (mushy) or watery[b] stools $\geq$ 25% of bowel movements[c]
4. Unsubtyped IBS—insufficient abnormality of stool consistency to meet criteria for IBS-C, D, or M[c]

[a] Bristol Stool Form Scale 1–2 [separate hard lumps like nuts (difficult to pass) or sausage shaped but lumpy].

[b] Bristol Stool Form Scale 6–7 (fluffy pieces with ragged edges, a mushy stool or watery, no solid pieces, entirely liquid).

[c] In the absence of use of antidiarrheals or laxatives.

Adapted from Ref. *(13)*.

In the Rome III classification, the FGIDs are classified into six major domains for adults. There are subgroups in the domains, but for the purpose of this text, I include only the subgroups in category C, "bowel" (Tables 1 and 2) *(14)*.

It is important to emphasize that pain is the defining criteria for the diagnosis of irritable bowel syndrome; if a patient has a change bowel habit characterized by loose stool without pain, then the patient has functional diarrhea.

The working group in Rome III also proposed subtyping patients according to the predominant stool pattern although this may not be very useful because symptoms change overtime (Table 3).

EPIDEMIOLOGY

IBS is a very common disorder that affects between 10 and 20% of adolescents and adults worldwide. In population-based studies, the prevalence of IBS in the USA is 10–15%, with a 2:1 female predominance. However, in referral populations, the female to male ratio is 4:1 *(15)*. It is important to emphasize the impact of life events in the incidence and clinical manifestations of gastrointestinal diseases, IBS, and chronic pelvic pain. In an academic setting at the University or North Carolina at Chapel Hill, Dr. Drossman *(16)* investigated the frequency of physical and sexual abuse amongst 206 women; 53% of women with a functional disorder had a history of sexual abuse compared to 37% of women with an organic disease, 13% of patients with a functional disorder had a history of physical abuse compared to 2% of patients with an organic disease. It is important to emphasize that in these patients, it is not appropriate to follow the policy of "don't ask, don't tell"; 59% of these patients had never discussed their history of abuse with health care providers, 33% had never discussed this history with anyone, and only 17% of the GI physicians knew about the history of abuse. Patients with a history of abuse were also more likely to have more severe abdominal pain and more a higher frequency of pelvic pain. As part of an epidemiological study of patients with irritable bowel syndrome, Walker et al. *(17)*. performed a study where a medical-trained interviewer administered a questionnaire to 60 women with IBS and

to 26 women with inflammatory bowel disease. Chronic pelvic pain was reported by 35% of patients with irritable bowel syndrome, but only in 13.8% of patients with inflammatory bowel disease. The most important predictor of IBS and chronic pelvic pain in these patients was the number of somatization symptoms; these patients were also more likely to have a history of current or past panic disorder; these patients were also more likely to have a history of current or past panic disorder, dysthymic disorder, childhood sexual abuse, and hysterectomy than patients with IBS without chronic pelvic pain or patients with inflammatory bowel disease.

DIAGNOSIS AND TREATMENT

Chronic pain syndromes represent a challenge to the clinician. It is important to limit investigations, make a diagnosis, and establish a treatment plan. The diagnosis of irritable bowel syndrome is a clinical diagnosis, and in most patients, there is no need to do extensive investigations. Determining which tests are indicated depends on whether the prevalence of the disease being investigated is higher in patients with IBS than in the general population; the prevalence of celiac disease in patients with IBS is 5% compared to 1% in the general population, therefore celiac serology may be considered in patients with IBS and diarrhea. However, routine testing for inflammatory bowel disease, colorectal cancer, gastrointestinal infections, thyroid disease, or lactose intolerance is not indicated *(18)*. To decide whether other investigations are indicated, it is important to determine whether the patient has "alarm symptoms" such as hematochezia, unintentional weight loss greater than 10 pounds, family history of colon cancer at a young age (<50 years old), fever, anemia, or severe chronic diarrhea. If any of these symptoms are present, then diagnostic tests are recommended. The tests should be tailored to the clinical situation; in general, the tests that are recommended in a patient with "alarm symptoms" are CBC, erythrocyte sedimentation rate, serum chemistry, thyroid tests, stool tests for infectious causes, colonoscopy, and breath tests for small intestinal bacterial overgrowth and lactose intolerance. In some patients, it is important to perform radiological studies such as CT enterography, CT of the abdomen, and pelvis or magnetic resonance studies.

The pharmacological treatment of patients with irritable bowel syndrome is determined by symptoms, and except for the $5HT_3$ receptor antagonists and the $5HT_4$ receptor agonists, the evidence to support its use is insufficient or of poor quality. Antispasmodic medications with anticholinergic or antimuscarinic effects are more commonly used in the treatment of patients with irritable bowel syndrome that have abdominal pain and diarrhea; however, most studies are small clinical trials of poor quality and short duration *(18)*. There are two types of antispasmodic agents: direct smooth muscle relaxation agents (e.g., mebeverine, pinaverine) and anticholinergic/antimuscarinic agents (e.g., dicyclomine, hyoscyamine). Antispasmodics with a direct effect on smooth muscle are not available in the USA; they are available in Canada, Mexico, and Europe. Even though the trials on the use of these agents are poorly designed, these medications used at the recommended doses appear to be effective in the treatment of patients with irritable bowel syndrome. The clinical trials on the use of dicyclomine and bentyl have a poor design and in general, do not show a significant clinical effect. There is only one clinical trial that showed that dicyclomine was effective in the treatment of patients with irritable bowel syndrome; however, in this trial *(19)* the dose of dicyclomine used was 40 mg po q.i.d., which is much higher than the recommended dose, and leads to significant side effects.

Bulking agents are used primarily to treat patients with constipation, although at times because of its capacity to bind bile salts, they are also used in patients with irritable bowel syndrome with constipation alternating with diarrhea. Bulking agents includes various forms of fiber and are divided into soluble types of fiber (e.g., psyllium, ispaghula husk, and calcium polycarbophil) and insoluble fiber (e.g., methylcellulose and corn fiber). Regardless of the type of fiber, the data to support its use are of poor quality; furthermore, some of these agents increase bloating and abdominal pain and are poorly tolerated by patients. Given this side effect, bulking agents are indicated for the treatment of simple constipation but not in the treatment in patients with irritable bowel syndrome where pain is a cardinal manifestation. Antidiarrhea agents such as loperamide are used frequently to treat diarrhea; the clinical trials on the use of loperamide in the treatment of patients with irritable bowel syndrome and diarrhea have shown that it is effective in decreasing the number of bowel movements and improving stool consistency; however, this agent does not relieve abdominal pain *(18)*.

The use of tricyclic antidepressants (TCAs) and serotonin re-uptake inhibitors (SSRIs) in the treatment in patients with irritable bowel syndrome is common even though the evidence to support their efficacy is limited. Tricyclic antidepressants are believed to decrease pain because of its effect on visceral hyperalgesia, these medications can also improve diarrhea because a frequent side effect is constipation. In clinical trials, the dose of TCAs is usually lower than the dose used for treatment of depression.

Because of the relevance that serotonin has in the function of the gastrointestinal system and because SSRIs have fewer side effects than TCAs, these medications are more commonly used by clinicians than TCAs; however, the benefit of these medications is not clear. Amongst the SSRIs, paroxetine may be the medication that has been investigated the most. Even though paroxetine improves quality of life, decreases rectal urgency, straining and sense of incomplete evacuation, it does not have a significant effect on pain *(20,21)*.

As mentioned earlier, the best evidence for efficacy of medications in the treatment of patients with irritable bowel syndrome is for $5HT_3$ receptor antagonists and the $5HT_4$ receptor agonists. These receptors are extensively distributed in the enteric nervous system and in peripheral afferents within the brain. These receptors help modulate colonic transit, intestinal secretions, and visceral pain. Alosetron is a $5HT_3$ receptor antagonist that is indicated for the treatment of patients with diarrhea-predominant irritable bowel syndrome that have not responded to other treatment modalities. Alosetron effectively improves pain by its effect on the central nervous system and also possibly by blocking peripheral afferent sensory pathways and improves diarrhea by its effect on small intestinal and colonic motility *(22)*. There were two 12-week dose-ranging studies, Bardahan's study *(23)* had 462 patients (335 female) and Camilleri's *(24)* had 370 patients (196 female), and two 12-week phase III studies that compared alosetron 1 mg b.i.d. versus placebo. In the first study by Camilleri et al. *(25)*, 647 women were enrolled, and in the second study also by Camilleri *(26)*, 626 patients were enrolled. There was also a 12-week European study by Jones et al. *(27)* comparing alosetron 1 mg po b.i.d. to mevebirine; in this trial, 623 women were randomly assigned to alosetron 1 mg b.i.d. or mebeverine 135 mg t.i.d. for 12 weeks. Alosetron was superior to placebo and to mebeverine; there was a statistically significant improvement in abdominal pain or fecal urgency and stool frequency and consistency. Based on these data, the FDA approved the use of alosetron for women with IBS and diarrhea,

this medication was not approved for men because in the clinical trials approximately 90% of the patients were women.

The commonest side effect of alosetron was constipation; about 10% of patients withdrew from the studies because of this. In the clinical trials, there were two cases of ischemic colitis (one of which was associated with *Escherichia Coli* O157:H7). By march of 2002, there were 84 cases of suspected ischemic colitis that had been reported to the FDA, alosetron was initially withdrawn from the market and subsequently approved for use with prescribing restrictions. The indication is "for women with severe, diarrhea-predominant IBS who have failed conventional IBS therapy." Overall, it is estimated that the rate of ischemic colitis and serious complications of constipation are 1.1 and 0.66 per 1000 patient-years of alosetron, respectively. More recently, Chang et al. *(28)* reported a phase II dose range study on the use of Alosetron in men with diarrhea-predominant IBS. In this study, 662 men that were diagnosed with diarrhea-predominant IBS according to the Rome I criteria were randomized to receive 0.5, 1, 2, 4 mg, or placebo b.i.d. for 12 weeks; adequate relief of abdominal pain and discomfort was significantly higher in men receiving alosetron 1 mg po b.i.d. compared to placebo (53 vs. 40%, $p = 0.04$), and all doses improved stool consistency. However, bowel urgency that was one of the symptoms that patients considered more troublesome did not improve, and the number of bowel movements also did not improve. The commonest side effect was constipation that was dose dependent, and one patient in the 0.5 mg b.i.d. had an episode of ischemic colitis.

The $5HT_4$ receptor agonist tegaserod is approved for "the short-term treatment of women whose primary symptom is constipation." The recommended dosage is 6 mg twice daily. Four well-designed clinical trials have evaluated the use of tegaserod in the treatment of constipation-predominant IBS, two placebo-controlled studies used two doses of tegaserod, either 2 mg po b.i.d or 6 mg po b.i.d. *(29,30)*, and two placebo-controlled trials using a dose of tegaserod of 6 mg po b.i.d. *(31,32)* that showed efficacy of this medication; there was improvement in global IBS score, patients had less abdominal bloating, abdominal discomfort, and improved bowel habits compared to placebo. More recently in a well-designed clinical trial, Nyhlin et al. *(33)* randomized 327 patients with constipation-predominant IBS to receive tegaserod 6 mg po b.i.d and 320 patients to receive placebo. This was a multi-center clinical trial on Nordic patients (Denmark, Finland, Iceland, Sweden, Norway, and Sweden), the odds ratio for satisfactory relief was greater in the tegaserod group with an OR of 1.78; however, the response rate was lower in these studies compared to other European, North American, or Asian studies.

Tegaserod is approved for short term, so patients use this medication on an intermittent basis. In 2005, Tack et al. *(34)* evaluated the efficacy of repeated treatment with tegaserod in patients that had previously responded to it. 2660 patients were randomized to receive either tegaserod 6 mg b.i.d. or placebo in a 4:1 ratio, 1191 patients that had at least a partial response and that had recurrence of symptoms within 12 weeks of discontinuation of treatment were re-randomized to tegaserod or placebo in a 1:1 ratio. Tegaserod was superior to placebo in the first treatment and in re-treatment. Given the cyclical nature of IBS, it is logical to use episodic treatment as needed; a response is usually seen within 1 or 2 weeks of starting treatment. The commonest side effect of tegaserod is diarrhea which occurs in about 9% of patients.

CONCLUSIONS

IBS is a significant cause of chronic pelvic pain, especially in women. These patients frequently undergo unnecessary tests including surgery, and the treatment of these patients can be frustrating both to the patient and the physician. When evaluating patients with irritable bowel syndrome, it is very important to obtain a thorough social history, and to treat these patients, it is important to establish a relation of trust with the patient. Reassurance and the rational use of tests and medications are crucial to have a positive outcome.

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9

Genitourinary Pain and Inflammation in Rheumatic Diseases

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Summary

Musculoskeletal and rheumatic complaints account for over 15% of patients' visits in a primary care setting. Although systemic rheumatic disease, in general, is uncommonly associated with lower genitourinary diseases and bladder dysfunction, the myriad of musculoskeletal and rheumatic complaints may co-exist in a patient, and it is important to be aware of more frequent associations. When performing a thorough history and physical examination, it is important to consider genitourinary manifestations of rheumatic diseases such as arthritis of lower spine, pelvis, or hips, spondyloarthropathies, Sjogren's syndrome, and fibromyalgia. Treatment is dependent on the specific disease process involved.

Key Words: Musculoskeletal and rheumatic diseases; lower genitourinary tract; bladder function; arthritis; spondyloarthropathy; sjogren's syndrome; fibromyalgia.

Contents

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OVERVIEW

A busy practitioner often has access to an enormous amount of medical information but little time to absorb this. As musculoskeletal and rheumatic complaints account for over 15% of patients' visits in a primary care setting, it is important to review the pertinent systemic rheumatic diseases associated with lower genitourinary tract. The primary role of the lower genitourinary tract is bladder function and control and its concomitant complications are complex, including local area infections such as urethritis or cystitis, and local area pain due to dryness, dyspareunia, pelvic pain, or problems with increased peripheral nociception. Bladder control, in particular, is dependent on complex neural circuits in the brain, spinal cord, and peripheral ganglia. This distinguishes the lower genitourinary tract from other visceral structure such as the gastrointestinal tract or cardiovascular system and may explain some of the common association with chronic pain such as fibromyalgia or autoimmune disorders such as Sjogren's syndrome *(1,2)*.

Rheumatic diseases are commonly classified as (i) primarily associated with articular or arthritic manifestation, (ii) systemic rheumatic disease, and (iii) non-inflammatory rheumatic disorders. Arthritis conditions can be localized or generalized and non-inflammatory such as osteoarthritis are truly systemic in nature with generalized inflammation such as rheumatoid arthritis, spondyloarthropathies, and many others. Systemic rheumatic diseases include systemic lupus erythematosis, Sjogren's syndrome, and others and are characterized by multisystem involvement with widespread inflammation. Finally, there are innumerable non-inflammatory disorders, which can be localized such as tendonitis, muscle strain, and other associated soft tissue problems or more widespread syndrome with fibromyalgia being the most common in the US population.

Although systemic rheumatic disease, in general, is uncommonly associated with lower genitourinary diseases, the myriad of musculoskeletal and rheumatic complaints may co-exist in a patient, and it is important to be aware of more frequent associations (Table 1). The following chapter will present the more common rheumatic conditions that can present with lower genitourinary complaints in males and females.

GENITOURINARY PAIN AND INFLAMMATION AND ARTHRITIS

History Taking in Patients with Arthritis

A complete history and physical examination is the most helpful diagnostic tool in the evaluation of patients with musculoskeletal complaints. Important antecedent history taking include recent illnesses or trauma, childhood or prior episodes of joint pain, and family history of arthritis or autoimmune disorder. Patients can provide diagnostic clues by describing the pattern or development of musculoskeletal involvement. It is important to delineate the number of joints and the time course over which a joint or musculoskeletal complaint is noted. This will help guide the approach to a differential diagnosis. An acute joint with redness and warmth over days may represent a potentially septic process. This would have an abrupt onset and may require a careful examination of an associated infectious process elsewhere, such as a urethritis. On the other hand, a single joint affected over 3–6 months time may represent a more chronic condition such as a seronegative spondyloarthropathy (SpA)

Table 1
Common Lower Genitourinary Problems and Associated Rheumatic Conditions

Rheumatic disorder	*Genitourinary manifestation*
Systemic rheumatic diseases	
Sjogren's syndrome	Irritable bladder
	Interstitial cystitis
	Vaginal dryness
Primarily associated with arthritis	
Spondyloarthropathy	Inflammatory bowel disease
Arthritis associated with infectious agent	
Reactive arthritis	Vaginitis
STD-related arthritis	Urethritis
	Circinate balanitis
Non-inflammatory conditions	
Fibromyalgia	Irritable bladder
	Interstitial cystitis
	Pelvic pain dyspareunia

that will require more information. It is also important to determine whether the patient experiences back pain, skin lesions, extra articular symptoms, or family history.

Spondyloarthropathies and Reactive Arthritis

An abrupt onset of joint symptoms would raise the possibility of acute bacterial infection or a reactive arthritis. Conditions of acute urethritis or vaginitis with migratory polyarthritis are commonly seen with nisseria gonorrhea, which will be discussed in detail elsewhere. Seronegative spondyloarthropathies is a heterogeneous group of diseases characterized by the presence of class I histocompatibility antigen HLA-B27, axial arthritis, inflammatory eye disease, and possibly urethritis. The spectrum of SpA includes ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease related, undifferentiated SpA, reactive arthritis, and Reiter's syndrome. In particular, Reiter's syndrome has the triad of conjunctivitis, urethritis, and asymmetric oligoarthritis. Reactive arthritis can present with acute polyarthritis following a urethral infection or dysentery. Current literature has now redefined Reiter's syndrome and reactive to be included under the category of reactive arthritis. Reactive arthritis can be triggered by either a gastrointestinal or a genitourinary infection. For gastrointestinal illness, the most common dysenteric pathogens are *Salmonella, Shigella flexneri, Campylobacter, Clostridium*, or *Yersinia*. For genitourinary infection, *Chlamydia, Neisseria gonorrhea*, and *Ureaplasma urealyticum* may cause reactive arthritis.

Conjunctivitis and, sometimes, acute anterior uveitis can be present in reactive arthritis and usually occurs at the same time as the symptoms of gastrointestinal or genitourinary infection. The joint symptoms, however, typically occur later in the disease course after the GU or GI infection has subsided. Thus, it is often difficult to culture the GU or GI system for signs of infection when a patient presents to the rheumatologist for joint pain as a critical time period has elapsed to detect infection.

Thus, a high index of suspicion at the time of GU or GI infection and subsequent culture data should be documented.

Other related extra-articular manifestations include circinate balanitis. These are characteristic lesion involving the glans or shaft of the penis and the cause is unknown.

Management

The principles of management of the infectious diseases associated with reactive arthritis including *Chlamydia, N. gonorrhea*, and *U. urealyticum* are similar to the management in those without arthritic complications.

SYSTEMIC RHEUMATIC DISEASES ASSOCIATED WITH GENITOURINARY DISORDERS

Sjogren's Syndrome

Primary Sjogren's syndrome is an autoimmune disorder affecting the lacrimal and salivary glands, resulting in decrease in the production of saliva and tears producing sicca symptoms (xerophthalmia and xerostomia). In the affected organs, the key histological feature is a focal or diffused lymphoid infiltration, predominantly represented by CD4 T lymphocytes. Extra-glandular involvement includes cutaneous, thyroid, respiratory, musculoskeletal, neurological, hematologic, reproductive, and urinary tract. Sjogren's syndrome can be a primary or secondary phenomenon.

Most common symptoms associated with Sjogren's syndrome include difficulty in swallowing or chewing, dental caries, enlarged parotid glands, and visual problems from the sicca symptoms. Less common problems include urinary tract symptoms that are similar to irritable bladder conditions, interstitial cystitis (IC), and vaginal dryness *(3)*. In the Rotterdam study, IC and Sjogren's syndrome was recognized as having a strong association; 28% of patients with IC had definite or probable Sjogren's syndrome. In a study by Haga et al., a case control was done to assess the impact of primary Sjogren's syndrome on reproduction and gynecological manifestations of 58 Sjogren's patients with 157 controls. In this cohort, Sjogren's patients reported more gynecological problems than the control group, including vaginal sicca symptoms, endometriosis, several episodes of amenorrhoea, and menorrhagia/metrorrhagia *(4)*. Other GU organ system affected in Sjogren's syndrome is the kidneys, which may include distal tubular renal acidosis, tubulo institial, or glomuerular dysfunction *(3,5)*. In a study by Bossini et al., clinical and morphologic characteristics of 60 Sjogren's patients were evaluated with kidney involvement, and overt clinical renal dysfunctional was rare but renal biopsies confirmed tubuloinstititial nephritis and glomerular disease in 9 out of 60 patients *(3,6)*.

Management

Unfortunately, there are no remitive therapies for Sjogren's syndrome, and patients are generally managed on the basis of individual signs and symptoms. In the setting of lower GU complications such as IC, individual patients should be managed traditionally. It is of more importance for the non-rheumatologist seeing such patients to inquire about signs and symptoms suggestive of systemic inflammatory diseases and refer to rheumatologists when the suspicion is high.

NON-INFLAMMATORY RHEUMATIC DISORDERS

Fibromyalgia

Fibromyalgia is a common musculoskeletal disorder affecting up to 2% of the general population. It is a chronic painful, non-inflammatory condition associated with fatigue, poor sleep, and multiple somatic complaints. In 1990, the syndrome was redefined by the American College of Rheumatology as a disorder of widespread pain and tenderness in greater than 11 of 18 tender point sites. The tender point sites have a sensitivity of 88% and specificity of 81%. The cause of fibromyalgia is unknown. Possible etiologic roles include sleep disorders, depression, and central sensitization; however, the evidence-based studies are evolving.

Patients with fibromyalgia often have signs and symptoms compatible with a number of other disorders or syndromes that are frequently viewed as "medically unexplained." Some of the disorders are listed in Table 2. Wesely et al. considers fibromyalgia within a spectrum of highly overlapping disorders which at times are difficult to separate into distinct categories *(7)*. In addition, each share a variety of associated symptoms such as chronic fatigability and have a high background rate of current or past mood disorders. Many of such patients are diagnostically labeled, and not primarily on their clinical signs and symptoms but rather on the diagnostic bias of the specialist they may be seeing. For example, the patient with myalgias, fatigue, bowel irregularity, tension headaches, and irritable bladder may be diagnosed with fibromyalgia by the rheumatologist, whereas a gastroenterologist may be more interested in the bowel symptoms and label the same person with irritable bowel syndrome. The specialist in genitourinary medicine may evaluate the same patient for irritable bladder or IC but fail to recognize the comorbidities of rheumatic disorders and bowel disease. A comprehensive diagnostic and integrated therapeutic approach is needed for all such patients including screening questions for attendant mood disorders such as depression, panic, and anxiety.

Table 2
Common Somatic Syndromes by Medical Subspecialties

Subspecialty	*Somatic syndrome*
Allergy	Multiple chemical sensitivity
Cardiology	Atypical chest pain
Dentistry	Tempormandibular joint dysfunction atypical facial pain
Ear, nose, and throat	Globus syndrome
Gasroenterology	Irritable bowel syndrome
	Non-ulcer dyspepsia
Gynecology	Premenstrual syndrome
	Chronic pelvic pain
Infectious disesease	Chronic fatigue syndrome
Neurology	Tension headache
Respiratory medicine	Hyperventilation syndrome
Rheumatology	Fibromyalgia

Adapted from Ref. *(7)*.

As evidence of these associations is the observation that many patients experience higher than normal incidence of lower genitourinary symptoms with fibromyalgia compared to other systemic rheumatic diseases. Most commonly, there is literature on the relationship between fibromyalgia and IC *(8,9)*. In a study of 60 fibromyalgia patients, 30 IC patients, and 30 control patients, there were similar increased pain sensitivity when compared to healthy individuals. This demonstrates significant overlap in symptomatology in patients with IC and fibromyalgia implicating increased peripheral nociception *(8)*. There are also survey and descriptive studies that demonstrate an increased association between patients with fibromyalgia and irritable bladder syndrome, pelvic pain, or dyspareunia *(1,8,10,11)*.

Therapy

The management of patients with fibromyalgia with or without signs and symptoms of lower genitourinary dysfunction is problematic. For the non-rheumatologist seeing such patients with irritable bladder, IC, unexplained pelvic pain, and dyspareunia, awareness of associated somatic disorders (Table 2) may allow for a more comprehensive diagnosis and permit other specialists to participate in managing non-genitourinary symptomatology. In general, all such patients should be screened for concomitant mood disorders and sleep disorders and treated when appropriate. Many practitioners encourage a holistic approach incorporating diet exercise and stress modifications, but results of such interventions are not evidence based. Medications aimed at curtailing the pain or central sensitization may help ease the symptoms of lower genitourinary tract; however, further research is needed.

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II Genitourinary Disorders Affecting Only Men

10 Testicular Pain

Acute and Chronic

Juan F. Uribe, MD

SUMMARY

Testicular pain is an assiduous visitor in the urological consultation. When it appears as an acute onset, it constitutes a medical emergency that needs proper evaluation and an immediate solution, sometimes by means of surgery. When it appears as chronic problem, it is a riddle that requires great knowledge to know the wide inventory of differential diagnosis, upon which the mechanisms of testicular pain are based on. Limited knowledge of options of differential diagnosis frequently implies mistaken diagnosis assignation to clinic onset that shares identical signs and symptoms but were originated in different diseases or physiopathology.

KEY WORDS: Pain; testicle; scrotum; urethra; orchialgia; dynias; orchitis; epididymitis; prostatitis; cancer; vasectomy; torsion; varicocele.

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HISTORY OF TESTICULAR PAIN

Testicular pain has worried humanity throughout the times. In old Greek mythology, testes were the preferred parts of the body for Gods to torment men. Gods shot arrows at men's testes when they wanted to punish them *(1)*.

Castration was a religious and medical practice over 3000 years old recorded in the Old Testament, in antiquity, children were castrated to obtain singers for choirs with childish voices, called *castratis*. Castrated men called eunuchs were employed in royal courts for the care of the king's harem. However, castration was also used to treat all types of testicular pathologies in particular inguinal hernias, abscesses, and chronic infections that caused untreated pain to patients who suffered from them *(2,3)*.

In 1703, Giovanni Batista Morgagni (1682–1771) was considered the father of European anatomy; in 1703, he was the first to describe a hydatid of testicle which bears his name. He was then Antonio Maria Valsalva's surgical assistant at the hospital of Santa Maria of the Morte in Bologna, Italy. Hydatid means "drop of water," and Morgagni died convinced that the rupture of these structures explained the genesis of hydroceles *(1,2,4,5)*.

In 1776, John Hunter, a English surgeon, made the first report of a case of testicular torsion and 70 years later French psychiatrist Louis Delasiauve, interested in the cases of histrionic patients, described the first case of torsion in a patient with abdominal pain and undescended testes. At first, he suspected this patient had an ectopic kidney. It was another 70 years before Louis Ombredanne, one of the founders of pediatric surgery described, in 1913, torsion of appendix of testes, and later Colt, in 1922, considered testicular torsion a surgical emergency *(1,2,4, 6–9)*.

Soon it was clear that despite the clinical importance of testicular torsion, it is not just the most common cause of orchialgia. The drama of this clinical onset can obscure the vast inventory of differential diagnoses that are being investigated. Future knowledge will be enhanced by the consideration and investigation of the biochemistry and the angio-architecture of the spermatic cord that seems by itself to be a secretor organ, as well as the most recent on origin, pathways, and neuromodulation of the pain *(10)*.

NEUROANATOMY OF THE SCROTAL CONTENTS

Sensorial innervations of the testes and epididymis are conducted by fibers, autonomic and sensorial, that travel through the spermatic cord. The somatic fibers of the cremaster muscle and the parietal and visceral layers of the vaginal tunica travel by the genital branches of the genito-femoral nerve (originated in L1–L2) and the ilioinguinal nerve that corresponds to the first lumbar nerve (L1). Nocioceptives fibers go to the testes, vas deferens, and epididymis with the sympathetic nerves that innerve each organ. Testicular nocioceptives fibers travel with the sympathetic plexus (T10–T12), whereas the deferential and epididymal nocioceptives fibers travel with the pelvic plexus (T10–L1) along the vas deferens. Alternative routes to the spermatic plexus of the autonomic type could exist that extend the transmission of the pain. If the pain was exclusively originated in the scrotal content by the way of the spermatic branches of the ilio-inguinal and genito-femoral nerves, a blockage of the cord would alleviate the pain in all the cases (Fig. 1) *(11–13)*.

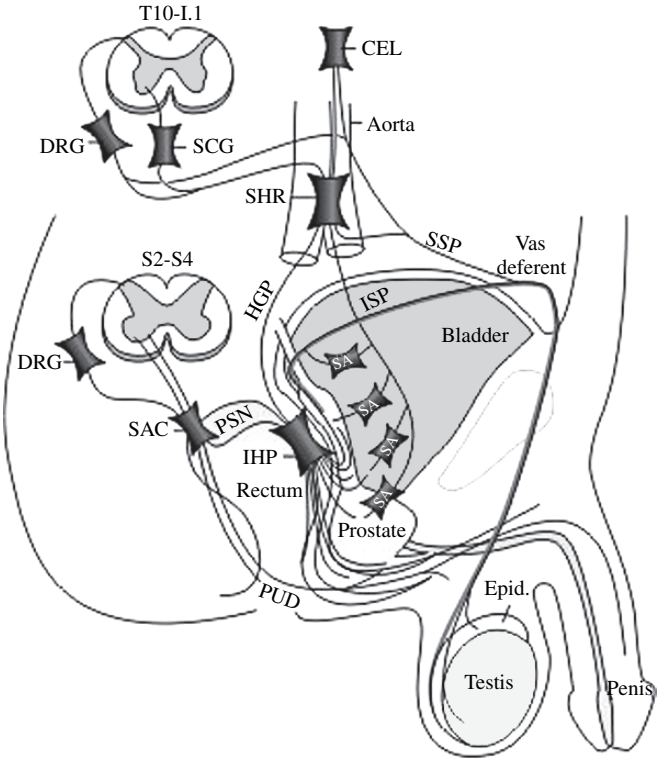

Fig. 1. Neuroanatomy of pelvis and scrotal contents. Epid, epididymis; CEL, celiac plexus; DRG, dorsal root ganglion; HGP, hypogastric plexus; SHP, superior hypogastric plexus; IHP, inferior hypogastric plexus; SSP, superior spermatic plexus; ISP, inferior spermatic plexus; PSN, pelvic splanchnic nerve; PUD, pudendal nerve; SAC, sacral plexus; SCG, sympathetic chain ganglion.

"ORCHIALGIA" DEFINITION

The term orchialgia often implies some degree of confusion as it suggests an exclusively orchial or testicular origin. In fact, any pain of intra-scrotal origin can be perceived in the lower part of abdomen, the internal inguinal ring, the penis, the back or the upper part of thigh, and not necessarily in the testicular body, whereas other extra scrotal pathologies radiate the painful sensation directly at testes and their vicinity. Usually, this pain is intermittent and gets worse with pressure on the scrotal content. Searching more descriptive terminology, the medical field has considered terms like escrotalgy, orchidynia, inguinalgy, epididymalgy, testalgy, testicular angina, chronic testicular pain (CTP) or chronic scrotal pain syndrome (CSPS), and "enigmatic syndrome," but all seem equally unable of conveying the complexity of this painful phenomenon *(14–18)*.

To understand orchialgia, it is necessary to understand the routes of the pain. There are three different classifications of pain: somatic or superficial, visceral, and neuropathic. Perhaps, testes and breast are the only organs of the body that participate in these three types of sensitivity. Because of their therapeutic implications, each one of these groups would have to assign, according to onset, the testicular pain that the patient suffers to suitably classify them *(18)*.

Pain Classification

- Somatic: Somatic pain receptors are in the skin, muscles, and joints. They can be subdivided into superficial, in which the stimulus affects the skin receptors, and deep, when the stimulated receivers are in muscular planes, connective tissue, or bone. The somatic pain is habitually acute and local; the patient does not have difficulty locating or describing it *(19)*.
- Visceral: The visceral nociceptors, because they are mainly composed by amyelinic afferent fibers, are activated by traction, distension, or ischemia. The pain is diffuse and misplaced, it has a significant independent component so it can be referred through a cutaneous area that shares the same pathway of innervation. The pain can be acute, subacute, or chronic *(19)*.
- Neuropathic: The original definition of neuropathic pain is "that which originates in injury or dysfunction of the nervous system." In this type of pain, the afferent peripheral nervous fibers respond to the painful stimulus by activating a biochemical cascade that includes potassium release, alteration of the sodium channels, and synthesis of prostaglandins and bradykinins. The prostaglandins, by themselves, elevate sensitivity of the nervous terminals to all substances producing pain; activation causes impulses from the stimulated terminals to spread across the dorsal horn of the spinal cord and other adjacent nervous terminals before it achieves a supraspinal neuromodulation. These terminals induce substance liberation like "P peptide" that causes vasodilatation and neuronal edema ending up in an increase in concentrations of histamine and serotonin in the extra-cellular fluid, sensitizing all neighbor nociceptors and ultimately causing an erratic dissemination of painful sensation, which generates the gallant narration of the painful picture by the patient. Furthermore, neural ectopic activity, particular to the patient's development, may cause an alteration of the expression of sodium channels. Patients relate hyperalgesia (dissociation between the magnitude of painful sensation and the painful stimulus), dysesthesia (difficulty in locating the area of the pain), and allodynia (pain with stimuli that is typically not painful) symptoms that culminate in being helpless to understand the clinical onset being presented. This repeated process explains the genesis of CTP *(18–25)*.

ACUTE TESTICULAR PAIN

By general definition, acute orchialgia occurs as pain lasting less than 7 days although it very often becomes an urological emergency of such magnitude that forces an immediate evaluation and treatment, conforming an urgency that has been denominated as "acute scrotum." Epididymitis is considered an exception in time, because, by definition, it is considered an acute diagnosis, with a less than 6 weeks progression *(18,21,26)*.

CHRONIC TESTICULAR PAIN

Chronic orchialgia is testicular pain that is constant or intermittent with more than 6 months duration. All causes of acute pain are potential causes of chronic pain when patients do not receive suitable diagnoses and treatment. The specialist who faces a patient with CTP often experiences frustration and discouragement because of the inability to determine a reliable etiology *(27)*.

The European association of urology, in its guides on chronic pelvic pain published in the year 2003, requires a distinction between four separate syndromes:

1. *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 epididymo-orchitis or other obvious pathology *(27)*.
2. *Testicular pain syndrome*: is the occurrence of persistent or recurrent episodic pain localized into the testes on examination that is associated with symptoms suggestive of urinary tract or sexual dysfunction. There is no epididymo-orchitis or other obvious pathology *(27)*.
3. *Post-vasectomy pain syndrome*: is a scrotal pain syndrome that follows vasectomy *(27)*.
4. *Epididymal pain syndrome*: is the occurrence of persistent or recurrent episodic pain localized in the epididymis on examination that is associated with suggestive symptoms of urinary tract or sexual dysfunction. There is no epididymo-orchitis or other obvious pathology *(27)*.

In men, other sources of chronic pelvic pain are described in addition to the urogenital, such as myofascial, musculoskeletal, gastrointestinal, and psychogenic pain *(28,29)*.

Chronic orchialgia must be classified as a painful syndrome of a neuropathy class, typically originated from an event with damage of a nerve that results in a chronic painful stimulus that involves the peripheral and central nervous system. A rational proposal, according to modern classification for chronic pain, is to consider orchialgia as "complex regional pain syndrome" (CRPS). "CRPS type II" (without damage of the nerve) would be the more common type, but also cases of "CRPS type I" (with damage of the nerve) cause testicular pain *(30–35)*.

DYNIAS

"Dynias" are described as a group of syndromes with focal chronic pain that show predilection by the orocervical and urogenital region, which includes glossodynia (pain in the tongue), carotidynia (pain in carotid zone), vulvodynia (pain in vulva), prostatodynia (pain in prostate), coccygodynia (pain in coccyx), penidynia (pain in penis), proctodynia (rectal pain, particularly proctalgia fugax), and of course orchidynia in orchialgia. The etiology is difficult to determine and, in many cases, the cause remains enigmatic (Tables 1 and 2) *(18, 30–35)*.

Table 1
Dynias

• Glosodynia (tongue pain)
• Carotidynia (carotid pain)
• Vulvodynia (vulvar pain)
• Prostatodynia (prostate pain)
• Coccygodynia (coccyx pain)
• Penidynia (penil pain)
• Proctodynia (rectal pain)
• Orchidynia u orchialgia (testicular pain)

Table 2
Causes of Testicular Pain

- Infectious causes
  - Acute pain
    - Epididymitis and epidymorchitis acute
    - Mumps orchitis
    - Testicular abscess
    - Fournier's gangrene
  - Chronic pain
    - Chronic epididymitis (brucellar, deep mycosis, leprosy, paludism, TBC, syphilis)
    - Chronic prostatitis
    - Malakoplaquia testicular
- Tumoral causes
  - Acute pain
    - Seminoma
    - Choriocarcinoma
    - Lymphomas
    - Leukemias
  - Chronic pain
- Traumatic and after surgery causes
  - Acute pain
    - Acute trauma
    - Dislocation of testis
  - Chronic pain
    - Post-Vasectomy pain syndrome (PVPS)
    - Nodous epididymitis
    - Orchialgia post-herniorrafias
    - Orchialgia post-varicocelectomy
    - Orchialgia post-spermatocelectomy
    - Orchialgia post-laparoscopic donor nephrectomy
    - Orchialgia post-needle biopsy of testis or semen aspiration procedures
    - "Self palpation" orchitis
- Torsional causes
  - Acute pain
    - Torsion of testis (extra-or intra-vaginal)
    - Perinatal torsion of the spermatic cord
    - Torsion of appendix
  - Chronic pain
    - Intermittent testicular torsion
- Vascular and immunologic causes
  - Acute pain
    - Aneurysms
    - Henoch-Schonlein purpura
    - Testicular: vasculitis
    - Acute idiopathic scrotal edema
    - Thrombophlebitis of pampiniform plexus
    - Testicular infarction
  - Chronic pain
    - Varicocele
    - Sweet's syndrome

- Intra-testicular arteriovenous malformation
- Intra-testicular hemangioma
- Splenosis

Neurologic/musculoesquelectic causes
  Acute pain
    - Tendinitis of insertion of inguinal ligament
    - Adductor tendinitis
    - Psoas spasm
    - Epilepsy
  Chronic pain
    - Sincrondosys
    - Pudendal nerve entrapment
    - Gluteal fibrositis
    - Phantom orchialgia
    - Lumbosacral radiculopathic pain
    - Koro's syndrome
    - Diabetic neuropathy
    - Pelvic floor tension myalgia

Drugs causes
  Acute pain
    - Mazindol
    - Amiodarone
    - Desipramine
    - Gadopentato dimeglumina (gadolinium)
    - Inipramine withdrawal
  Chronic pain

Miscellaneous causes
  Acute pain
    - Pelvic congestion
    - Appendicitis
    - Meconium periorchitis or meconium vaginalitis
    - Ureteral stones
    - Obstruction uretero-pelvic
    - Retrocaval ureter
    - Retroperitoneal fibrosis
    - Hidronefrosis
    - Constipation
  Chronic pain
    - Inguinal and femoral Hernias
    - Retractile testis
    - Hydrocele
    - Epididymal cyst (Spermatoceles)
    - Hyperuricemia
    - Macroorchidism
    - Microlithiasis testicular
    - Albuginitis constrictive
    - Multiple myeloma
    - Sarcoidosis
    - Abdominal neoplasm
    - Cirrhosis

SUBACUTE TESTICULAR PAIN

Between the 7 days (acute pain) and 6 months (chronic pain) is left a wide span of time for the pain that has been labeled as subacute and that can arise from anyone of the causes reviewed in this chapter.

CLASSIFICATION OF TESTICULAR PAIN

For its study, it is necessary to divide the causes of testicular pain into acute and chronic. To understand better, these two major groups are subdivided into eight subgroups according to the etiology of the pain *(18)*.

Group 1: Infectious causes of testicular pain (acute and chronic)
Group 2: Tumor causes of testicular pain (acute and chronic)
Group 3: Traumatic and post-surgery causes of testicular pain (acute and chronic)
Group 4: Torsion causes of testicular pain (acute and chronic)
Group 5: Vascular and immunologic causes of testicular pain (acute and chronic)
Group 6: Neurological and musculoskeletal causes of testicular pain (acute and chronic)
Group 7: Pharmacological causes of testicular pain (acute and chronic)
Group 8: Miscellaneous causes of testicular pain (acute and chronic).

Infectious

Acute Pain

Epididymitis and Epididymo-orchitis Acute. Infections of the scrotum and its content are the most frequent cause of acute pain in all ages, with the exception of prepubescent boys where the incidence of acute epididymitis is smaller. Nevertheless, in this age, infection is responsible for as many as 35% of the cases of acute scrotum in the youth with increasing numbers for the adults, particularly men over the age of 50. The infectious etiologies are bacterial (primarily), viral, mycobacterium, fungi, or sterile inflammation of epididymis that only appears in children *(36,37)*.

The patient may present a gradual onset of pain accompanied by dysuria, urethral drainage, history of recent surgery or urethral catheterization, recent urinary tract infection, or history of urinary malformation. While urinary symptoms are common, it is not an indispensable rule, because an epididymitis often exists in the presence of sterile urine *(38,39)*.

Acute epididymitis is often bacterial infection caused by an *Escherichia coli*. Therefore, additional data can be the history of anal intercourse. In adolescents until the age of 35, one must also consider ascendant infection from *Neissenia gonorrhoeae* or *Chlamydia Trachomatis* with the history of urethral symptoms along with a particularly painful epididymitis *(40)*.

In acute scrotum associated with urinary symptoms, an infectious process must be considered, and when it has related symptoms, such as nausea or vomiting, testicular torsion must be considered. The pain of an infectious cause is generally visceral, but it can have somatic elements, specifically in cases of cellulites of the scrotum *(3,18)*.

Throughout history, the ability to differentiate testicular torsion, which implies an urgent surgical solution, from testicular infection, which can be medically treated, has perplexed us. In 1934, at St. Albans naval hospital in Brooklyn, New York, D. Donald

Prehn made an interesting clinical observation: testicular pain of the sailors affected by gonococcus epididymitis improved when the affected testis was elevated, but in two cases, the pain worsened; in both patients, when they were surgically explored, the result was testicular torsion. Ergo, the origin of the mythical "Sign of Prehn" *(41,42)*. Another important sign that differentiates epididymitis from testicular torsion is the presence of the cremasteric reflex in epididymitis and its absence in torsion *(43,44)*. Orchitis is developed by direct spread in 20–40% of the cases of epididymitis, which increases the inflammation and pain *(42)*.

Mumps Orchitis (Primary Orchitis). In children, the most frequent cause of atraumatic orchitis without epididymitis but with severe testicular pain is infection by the virus of mumps or "infectia urliana"; as an acute clinical onset, it has significant severity by virtue of the size accompanying the inflammation in the interior of the testis that triggers an authentic compartmental syndrome on the testicular pulp with a high risk of secondary atrophy. Similarly, mumps in post-pubertal males is associated with a 40% incidence of orchitis, bilateral in 14–35% of cases *(42, 45–47)*.

Testicular Abscess. Another cause of testicular pain that belongs to the group of acute infectious processes that must be taken into consideration is the "testicular abscess". It is also a complication of a bacterial epididymo-orchitis in adults or, a torsion not being diagnosed, trauma or systemic infections, such as scarlet fever, influenza, and typhoid fever, in children. When such illnesses have testicular involvement, it is one condition that is particularly inflammatory and painful *(46,48,49)*.

Fournier's Gangrene (Spontaneous Gangrene). It is a necrotizing infection with direct involvement or secondary extension to the scrotum. Inflammation is serious, but it is a relatively painless condition as the fasciitis destroys the nervous terminals of the skin *(42,46)*.

Chronic Pain

Chronic Epididymitis or Epididymo-orchitis. It is a perpetuation of infectious agents or certain types of germs that, by a patient's physiopathology, cause chronic infections and are responsible for acute scrotum. It is important to consider the simplest criteria to diagnose a chronic epididymytis, namely prolonged pain, independent of the presence or absence of edema or associated congestion. The indurations and atrophy can be additional later signs that accompany the clinical picture *(49–57)*.

Other infections responsible for epididymitis or epididymo-orchitis and chronic orchialgia are as follows:

- **Brucellar epididymo-orchitis** was detected in 12.7% male patients with brucellosis. The most common symptoms were pain (94%) and swelling (82%).
- **Deep Mycosis**, actinomycosis, histoplasmosis, coccidioidomycosis, and equinococosis.
- **Testicular leprosy** is cause of acute epididymo-orchitis and soon chronic following the phases of the disease (vascular, interstitial, and obliterative). The pain appeared in 68% of the patients, and testicular compromise is more frequent in the lepromatose variety (62%) versus the dimorphic (30%).
- **Testicular paludism**, the malaria by falciparum can present an onset of acute testicular inflammation and pain.
- **Genital tuberculous with testes compromise** produces inflammatory, chronic, and suppurative changes with fistulas in the skin of the scrotum.
- **Equistosomiasis or filarial orchitis** is produced by the microfilaria loa-loa that usually is unilateral.

- **Granulomatous orchitis**, painful unilateral testicular enlargement in middle-aged men. Pathogenesis and etiology: unknown. Some speculate that the disease may have an autoimmune basis.
- **Syphilitic orchitis**, *Treponema pallidum* can trigger a testicular aspect indistinguishable of a tumor.

Chronic Prostatitis. It must be mentioned that, in chronic prostatitis, testicular pain is highly prevalent, in addition to penile pain and pain with ejaculation. This includes the "chronic pelvis pain syndrome" types IIIa (with leukocytes) and IIIb (without leukocytes), according to the classification of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) *(27,58,59)*.

Testicular Malakoplaquia. Observed in elder patients, it is denoted by a painful increase in the testicular size and is diagnosed only through a biopsy by which the bodies of Michaelis Guttman can be seen *(18,60)*.

Tumoral

Acute Pain

The tumors of testes and para-testicular structures can appear like an acute scrotum in about 10–15% of the cases. An old medical aphorism states that "when a greater injury exists after a minor trauma, a tumor must be discarded." During the examination, the testis is noted to be increased to a painful size, and it can be confused with an epididymo-orchitis or testicular torsion. In literature are reported different cases of tumors that began with painful onset. One such report was that a subcapsular hematoma causes pain especially in patients diagnosed with choriocarcinoma with early vascular invasion, creating fragile structures with high tendency for bleeding *(61–63)*.

Besides the classic seminomatous and non-seminomatous germinal tumors, others less commonly involving the testes, its coverings, and the cord must be considered, including lymphomas and leukemias more frequent in children. Seminomas, lymphomas, and leukemias are masked like an orchitis. The testicular pain is visceral and somatic *(18,64,65)*.

It is necessary to mention that children born with undescended testes have increased risk for testicular malignancy. Testes tumors usually develop during puberty and thereafter although there are reports of tumor development before 10 years of age. Approximately 10% of testicular tumors arise from undescended testes. The incidence of a testicular tumor in the general population is 1 in 100,000, and the incidence of a germ cell tumor in cryptorchid men is 1 in 2550; therefore, the relative risk is approximately 40 times greater than the general population. The pain assessment in these patients can more closely resemble an acute abdomen than an acute scrotum *(44,66–68)*.

Chronic Pain

Chronic orchialgia in the diagnosis of a testicular tumor is not so strange in health systems in underdeveloped countries or communities not sensitized to the early diagnosis of testicular cancer in young men. Seminomatous and non-seminomatous tumors can present progressive necrosis of testicular tissue that produces secondary inflammation and hydrocele with a slow increase in pain. There are reported tumors of slow growth, like leiomyomatosus proliferation of the epididymis, mesothelioma of the vaginal testicular, paratesticular rhabdomyosarcomas, and adenomatoids tumors. Where a culture of prevention does not exist, it is not rare that diagnoses of testicular

tumors are delayed, after causing months of testicular pain, with cases reported of up to 5 years of evolution without a suitable diagnosis *(18, 61–63)*.

Traumatic and After Surgery

Acute Pain

Trauma must be considered in all the ages as cause of acute pain. The first cause of trauma are aggressions with projectile of fire gun, white arms, and forceful objects, followed by trauma, traffic accidents, sport accidents, specially falls astride, and occupational accidents. The severity oscillates between the simple organ contusion to the crushing testicular (shrinking testis). A force of 50 kg is required to tear or break the albuginea tunica *(42,69)*.

The cause for the pain is a traumatic epididymitis, which classically appears hyperemic; on the ultrasound however, there are other injuries that aggravate pain, such as hematoceles or intra-testicular hematomas, tear of the albuginea, lacerations of testes or fractures that require surgical exploration. The type of pain is a mix of visceral pain produced by direct trauma to organ and somatic or superficial pain like the one caused by wound of the scrotum.

Accurate diagnosis and promptness to repair led to saving of the testicle, with preservation of testicular parenchyma and hormonal function. They also prevent delayed complications associated with missed testicular ruptures such as chronic pain, atrophy, and orchiectomy *(46,69,70)*.

An uncommon condition also causing severe pain is "Dislocation of the testis." It is the result of trauma producing damage or avulsion of fascias surrounding testis and/or of gubernaculum testis. The following sites of breakup are reported: Superficial Inguinal (45%), femoral (5%), pubic (18%), penile (8%), inguinal channel (8%), inferior abdominal (4%), superior abdominal (2%), acetabular (4%), perineal (4%), and crural (2%) (Fig. 2) *(18,71)*.

Any surgery on the genital area or of the scrotum can trigger acute, subacute, or CTP by different mechanisms that include surgical wound, injury of nerve branches, inadequate healing and edema, and other complications derived specifically for each one of procedures.

Chronic Pain

The same traumatic situations described in the section of acute pain are potential sources of persistence leading to chronic pain. The healing process, calcifications, chronic inflammation, and secondary hydrocele can explain the origin of chronic pain. In other cases, repeated surgical trauma is the cause of the testicular pain as in case reported by Negri et al., about a patient with imperforate anus who developed untreatable testicular pain after 14 attempts of surgical correction of the anal malformation *(72)*.

Post-Vasectomy Pain Syndrome. The vasectomy is registered as cause of testicular pain in a variable percentage between 33 and 56% of patients. Nevertheless, a genuine PVPS is developed in already 10% of patients post-vasectomy. Other names for this syndrome include post-vasectomy orchialgia *(73)*, late post-vasectomy syndrome *(74)*, congestive epididymytis *(75)*, CTP *(76)*. Now, the syndrome is generally recognized by the term post-vasectomy pain syndrome (PVPS) *(77)*. The classic post-vasectomy findings can be divided into early, intermediate, and late changes.

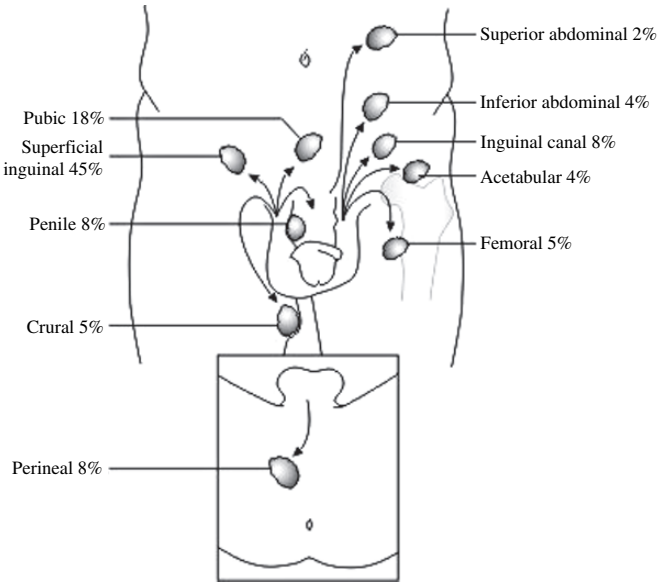

Fig. 2. Dislocation of testis. Sites of breakup: superficial inguinal (45%), femoral (5%), pubic (18%), penile (8%), inguinal channel (8%), inferior abdominal (4%), superior abdominal (2%), acetabular (4%), perineal (4%), and crural (2%).

Early Post-Vasectomy Changes. Increase in pressure: Section of vas deferens cause increased luminal flow pressure of seminal fluid, such increase in pressure is transmitted to the organs source of flow—the testes, epididymis, and efferent ducts.
Intermediate Post-Vasectomy Changes.

- **Over-whelms the dilatory and absorptive capacity of ducts**: The fluid within the obstructed ejaculatory system overwhelms the dilatory of ducts and absorptive capacity of the epididymytis and vas efferent.
- **Macrophages infiltration**: In response of fluid excess, macrophages begin to infiltrate the epididymis and accumulate in high numbers.
- **Antisperm antibodies**: The presence of large numbers of phagocytes and the possibility of interstitial leakage sets up an autoimmune state with chronic inflammatory cells that digest spermatozoa and present antigens for antibody production. At 1 year after vasectomy 60–70% of men have antisperm antibodies present in serum. This suggests that antisperm antibodies may play an important role in the pathology of PVPS that could explain the chronic inflammation like autoimmune process.

Late Post-Vasectomy Changes. Late changes represent the body's effort to repair the testicle from secondary damage to increasing pressures. Although these alterations may occur earlier in some, the majority occur late, after all efforts to manage the increasing pressure have been exhausted. Generally, these lesions are asymptomatic:

- Epididymal blowouts.
- Vasitis nodosa.

- Sperm granulomas: It has been shown that an absence of these lesions, particularly sperm granulomas, may predispose patients to PVPS. Once sperm has dissected through the muscular wall of the vas deferens and into the adventitia, the next step is extravasations into the interstitial space. As sperm are broken down by macrophages and lymphocytes, sperm components stimulate antigen-presenting cells which, in turn, initiate the cytokines that activate branches of the chronic inflammatory pathway. Activation of fibroblasts through cytokine release stimulates fibrosis, and a sperm granuloma is formed. Sperm granulomas also form in response to leakage of sperm secondary to epididymal blowouts.

PVPS in Closed-Ended Versus Open-Ended Vasectomy. PVPS in closed-ended versus open-ended vasectomy studies reported on their comparison of closed-ended vasectomy to open-ended vasectomy and found that 97% of the patients who underwent open-ended vasectomy developed sperm granulomas and 4% of patients with closed-ended vasectomy developed granulomas. Sperm granulomas are benign and their formation should be encouraged through the open-ended use of vasectomy to reduce the risk of PVPS. In fact, patients with PVPS generally do not have sperm granulomas, suggesting that PVPS is caused in part by the lack of to pressure relief.
Pain After Vasectomy Theories. Multiple pain explanations are possible:

- Epididymal congestion.
- Painful spermatic granuloma.
- Nervous entrapment of healing.
- Ejaculatory derangement. One exiting theory that includes anatomic derangement during ejaculation is likely responsible for PVPS. In post-vasectomy patients, the epididymis is trapped in the middle of two opposing forces when ejaculation occurs. The efferent ducts and the initial segments of the epididymis are lined with smooth muscle cells that contract during emission and ejaculation. The vas deferens also contracts in response to the associated noradrenergic and stretch stimuli. This results in movement of fluid from the testicle into the tail of the epididymis with simultaneous retrograde flow from vassal contractions into the great volume epididymis. In the absence of sperm granuloma, pain is due to the increase in itraluminal pressure, without an "escape valve."
- Depression post-vasectomy: It has been mentioned also like a cause of the pain, the development of a new depression post-surgical contraception in 1% of patients.
- Complication after vasectomy: The chronic pain is more frequent in patients that presented complications after surgery like hematomas or infection and the pain can oscillate between a slight annoyance to permanent pain with final treatment of orchiectomy or epididymectomy *(16, 73–82)*.

Nodous Epididymitis. It is a delayed complication after vasectomy. Represents an effort of additional repairmen after the rupture of ducts by pressure increase caused by the surgery. It implies chronic pain and worse of PVPS *(82,83)*.

"Self-Palpation" Orchitis. Patients who find pleasure in the manipulation of their scrotum or patients obsessed with testicular selfexamination in search of cancer can trigger a chronic painful inflammation *(13,16)*.

Orchialgia Post-surgery.

- Post-herniorrhaphy: After correction of inguinal or femoral hernias with extensive dissection, trauma of spermatic cord can persist a residual neuralgia. As well it is applied for any surgery with incision on the inguinal region by commitment of branches of the

ilioinguinal nerve that is the first lumbar nerve, which penetrates to the aponeurosis of the internal oblique muscle up of the ring superficial inguinal *(84,85)*.

- Post-varicocelectomy: The testicular pain can appear after inguinal correction by inguinal, subinguinal, or high ligature techniques with injury of nerve branches of ilioinguinal or genito-femoral during the dissection of the muscle to cremaster, by trapping of the branches in the suture, or by the process of healing itself. Another mechanism of the orchialgia post-varicocelectomy is passive congestion of epididymis and/or the testicle by the sudden decrease of the venous return.
- Post-spermatocelectomy: The incisions on the scrotal area produce acute pain but healing processes and hyperemia post-surgery could produce CTP.
- Post-orchidopexy: Dissection of spermatic cord and testicular fixation, sometimes forced, can cause chronic pain in these patients.
- Post-partial orchidectomy: "Epididymal sparing bilateral simple orchiectomy" (BSO) is an esthetic alternative to standard BSO. Fragment post-surgery can be source of post-surgical pain *(86)*.
- Post-needle biopsy of testes or semen aspiration procedures for infertility: Trauma caused for fertility procedures can produce acute, subacute, or chronic pain.
- Post-laparoscopic donor nephrectomy: Ipsilateral orchalgia has been reported in up to 9.6% of men following laparoscopic donor nephrectomy. The etiology remains unclear but may injure the sensory of the testicle during dissection of the periureteral tissue or transection of the spermatic cord *(87)*.

Torsional

Acute Pain

Torsion of intra-scrotal elements is the etiologic group that demands greater diagnostic ability and fast intervention of surgeon because irreversible ischemia of parenchyma testicular begins 4 h from that spermatic cord has been under occlusion. The maximum limit for intervention is of 8 h before it occurs a definitive alteration of the size testicular *(44, 88–90)*.

The type of pain is visceral with autonomic manifestations associated. Different studies have demonstrated that testicular torsion is not the first diagnostic option in the acute scrotum and that a great majority of suspicious onset can be solved without surgery, even between children and adolescents where it is possible to assume torsion as more frequent origin. Urgent torsion is surpassed by two clinical problems of medical handling as torsion of testicular appendix and epididymitis *(4,46,48)*.

Torsion of testes. Torsion of testes appears in two forms: intra-vaginal and extravaginal. Global incidence of torsions is 1 in 4000 men younger than 25 years and as cause of acute scrotum is 27% according to the analysis of Hawtrey *(88)* in 13 studies with a total of 1327 patients. The intra-vaginal abnormality, less frequent, appears in newborn up to 15 months, 72% of those torsions are intra-uterine. The onset must be suspected in infants with irritability, accompanied with nauseas and vomits by irritation of celiac plexus, the final result of ischemia on parenchyma is denominated "blue balls" with testes with little saving possibilities *(87,88,91)*.

The extravaginal abnormality denominated as "bell-clapper deformity" is the most frequent onset in emergency rooms, there is an inadequate fixation of vaginal testicular over spermatic cord that allows testes to turn freely on their axis; Ceasar and Kaplan found abnormality in 12% of autopsies demonstrating that the anatomical abnormality is more frequent than clinical manifestation of the disease *(90)*.

The trigger factor of torsion is the increase of weight of testes that occurs in the puberty, and detonating of the pain is generally defensive muscular (cremaster) spasm later reinforced by ischemia in the twisted cord *(91)*.

The testicular pain of visceral origin is accompanied by symptoms of autonomic nervous system, usually at the beginning pain is acute, but in some infants can be gradual, intermittent, or even so tenuous that it happens unnoticed. It can have irradiation to ipsilateral abdomen quadrant, and urinary irritatives symptoms usually are not present. In physical examination, the absence of cremasteric reflex is a good indicator of testicular torsion *(18,43,44)*.

Classically, when torsion occurs, surface of each testis turns toward the midline. For detorsion of the cord, a rotational effort should be made in the opposite direction. Examiner should try to twist or "unscrew" the testis in any direction (usually outward, toward the thigh) and then in the opposite direction if first attempt was unsuccessful.

When detorsion is successful, the testes "flip" to different rotation and pain relief may be almost instantaneous, with the cord appearing to lengthen and the testes dropping into the scrotum. Manual detorsion may not totally correct the rotation, and prompt surgical exploration usually is still indicated. However, when the patient becomes almost immediately comfortable, it can be assumed that blood flow to testis has been restored, at least in a significant degree *(44,92)*.

Other consideration deserves the great frequency of acute torsion of cryptorchidism testis that is explained by the abnormality of testicular mesentery and that can be associated to 64% with a germinal tumor. The clinical onset corresponds more to an acute abdomen than to an acute scrotum *(44,93,94)*.

Perinatal Torsion of the Spermatic Cord. Testicular torsion can happen in prenatal period (months, days, weeks before or even during the childbirth) or during postnatal period. The most important difference is that prenatal torsion is intra-vaginal, it does not imply one "bell-clapper deformity" and is a no painful pathology. Postnatal torsion has complete elements of extravaginal torsion, including genital sensitivity and obligation of quick surgical correction if diagnosis is opportune *(44,95)*.

Torsion of Appendix of Testes. Torsion of testicular appendix is a differential diagnosis in acute testicular pain with or without inflammation. It happens according to Hawtrey *(88)* in 32% as cause of acute scrotum. It is generally unilateral although there are described cases of synchronic appendix torsions. It is more frequent between 7 and 12 years but it can happen in adults, as well *(88)*.

Four possible intra-scrotal appendixes make torsion:

- Hydatid of Morgagni: testicular appendix is a remanent of Mullerian conducts, responsible for 92% of appendix torsions.
- Haller's organ: is appendix of the head of epididymis or is a Wolffian remanent and it contributes with 7% of torsions.
- Giralde's organ: appendix of vas deferent also called "paradidymis" or "innominade organ" is a Wolffian remanent, responsible for 0.7% of torsions.
- Vas aberrans: mesonephric remanent located in joint between body and tail of epididymis, responsible for 0.3% of torsions *(4)*. (Fig. 3)

The patient with testicular appendix twisted can have previous history of intermittent pain even for months; during the episode can present with symptoms of autonomic nervous system; in physical examination exquisite sensitivity is frequently felt in the upper portion of testes; and clinical manifestation is complete when exists in the

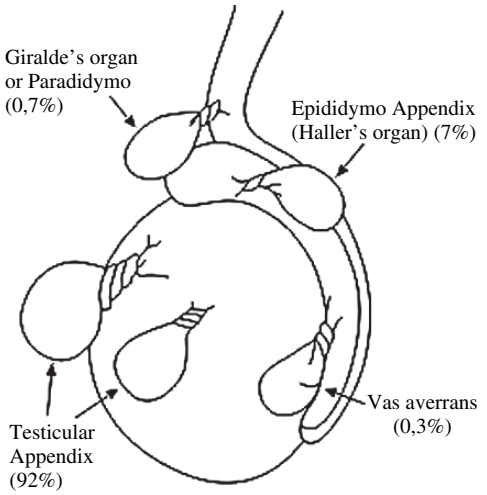

Fig. 3. Hydatid of Morgagni: testicular appendix. Haller's organ, head of epididymis appendix; Giralde's organ or paradidymis or innominade organ, vas deferent appendix; Vas aberrans, tail of epididymis appendix.

scrotum a "blue dots sign" that is pathognomonic. Unlike clinical findings between torsion of testes, the patient with torsion of appendix has a cremasteric reflex remaining. To have conscience of this diagnosis is essential for the physician because of the possibility of a no surgical handling. The presence of a pedunculated mass with hypoechoic areas, in testicular ultrasound usually in the superior portion of testes, can help diagnosis *(18,46, 96–99)*.

Chronic Pain

In this group, intermittent testicular torsion (ITT) must be considered. The most common presenting features were severe pain of rapid onset and solution with or without nausea and/or vomiting. Patients that id an episode of acute testicular torsion had a previous history of intermittent pain that solves by itself and corresponds in most of the cases to episode of torsion with spontaneous detorsion. A history of acute recurrent pain, with change in vertical axes or horizontal position of testes observed previously by patient or his parents with absence of pain at the time of the examination must make them think about this diagnosis. Studies in dogs have demonstrated that intermittent torsions imply turns in spermatic cord of 270° or less with 90° of turn ischemia leading to necrosis in 7 days, while with 1440° necrosis happens in 2 hours. Investigators have reported recurrent torsions even in testes previously put under orchidopexy *(100–104)*.

Vascular and Immunologic

Acute Pain

Vascular, immune, or autoimmune pathologies usually produce testicular pain of predominant visceral type.

Aneurysms. Aneurysms of the abdominal aorta, the iliac artery, or the testicular artery can begin initially as painful problem. Finding of pulsating mass will guide the

diagnosis that can be confirmed by Doppler ultrasound. Also severe testicular pain has been reported during episodes of dissection of aortic aneurysm *(105–107)*.

Henoch–Schonlein Purpura (HSP-Acute vasculitis). It is a systemic vasculitis, the most common in children under 10 years. In non-renal genito-urinary presentation, the syndrome may come along with scrotal pain and swelling that are part of the systemic condition, the most frequent non-renal genito-urinary symptoms reported in children with HSP, occurring in about 13% of boys evaluated. The diagnosis is difficult when cutaneous manifestations are after the abdominal manifestations of disease and clinical onset is confused with testicular torsion *(44,46,108,109,109A)*.

Testicular Vasculitis. It is a difficult diagnosis. In general, it is part of a systemic condition of a autoimmune disease like polyarteritis nodosa with compromise of medium and small arteries of testes and more rarely of Goodpasture syndrome; often it is confused with a epididymitis because it appears with an intense acute pain. The only method that allows an accurate diagnosis is nuclear magnetic resonance. Because of its characteristics, it is also confused with testicular neoplasia *(110–112)*.

Acute Idiopathic Scrotal Edema. It is a self-limited condition, usually painless but sometimes so dramatic and confused because of the edema that must be considered as differential diagnosis from other pathologies. Fever is not present, and scrotal tenderness is usually minimal, but pruritus may be significant. Although the process is considered to be idiopathic, insect bites, allergic or chemical dermatitis, trauma, and other known potential causes of scrotal inflammation may be responsible but undiagnosed *(44,113)*.

Thrombophlebitis of Pampiniform Plexus. It is an acute condition with intense pain that resembles torsion of testes or testicular appendix. It is more frequent in patients with dilatation of pampiniforme plexus *(113,114)*.

Testicular Infarction. Usually, it is segmentary. It is secondary to other pathologies with inflammation and pain. The initial onset may be similar to testicular torsion with a sudden and lancination pain, but it is also described in patients with falciform anemia or septic embolus during a bacterial endocarditic. There have been reported ischemic orchitis secondary to severe infectious epididymo-orchitis and less common others as embolic testicular infarction secondary to non-bacterial thrombotic endocarditis in Wegener granulomatosis. Ultrasound image in testicular infarct can be confused with tumor *(115–117)*.

Chronic Pain

Varicocele. These were already mentioned before varicocelectomy and thrombophlebitis of pampiniform plexus as causes of acute or CTP. Pain is more frequent in men between 15 and 25 years old, but it has been described that pain might begin in any age in patients with venous malformation. Relation with the magnitude of pain and degree of varicocele, size of testes, or alterations in parameters of semen has not been found. Painful of varicocele oscillates between sensation of weight and annoyance to real orchialgia. Mechanisms of pain were submitted to discussion but influence the venous stasis, incompetent valves and force of terrestrial gravity on erect position increases testicular congestion.

Venous pathology is more frequent in the left side and in examination is touched classic “bag worms.”

Varicocele intratesticular can be or not be associated to varicocele extratesticular. The difference is that first it produces greater testicular congestion and therefore more

pain. Descendent colon distended with feces, and phenomenon of "nutcracker" of the left renal vein between superior mesenteric artery and the aorta could produce transitory obstructions of the left testicular vein with episodes of pain *(42,48,118,119)*.

Sweet's syndrome. It is a neutrophilic dermatosis with history of recurrent fever, oral aphtas, phlebitis, pneumonitis, arthritis, and orchitis with chronic pain *(120)*.

Intra-testicular Arteriovenous Malformation. It is an uncommon and benign condition, that could be the source of pain. Diagnosis is with color dopler U.S. that shows the characteristic image of arterialized venous spectral waveform *(42)*.

Intra-testicular Hemangioma. It is a diagnosis differential of previous condition and it could be a cause of orchialgia *(42)*.

Splenosis. Dissemination of spleen tissue can include the inguinal region and cause severe testicular pain that is only alleviated with the removal of ectopic tissue *(121)*.

Neurological and Musculoskeletal causes of pain

Acute Pain

Acute pain caused by muscular or neurological abnormalities implies extragenital origin, and although any of the muscular or ligamentary insertions is a potential source of pain in the genital area, three acute sources must stand out as they can become chronic:

Tendinitis of insertion of the inguinal ligament.

Adductor tendinitis.

Spasm of the muscle psoas.

Epilepsy: Cerebral disrrhythmia specifically, the denominated "abdominal," cause testicular paroxistic acute pain as a main manifestation. Convulsions are expressed as intense genital pain and they yield to the use of common anticonvulsive *(122,123)*.

Chronic

Synchondrosis. It is reported in the medical literature that synchondrosis of transition between the thoracic and lumbar vertebrae (T12-L1) or in the joint lumbo sacral (L5-S1) is cause of chronic orchialgia with confusing previous clinical manifestation *(124)*.

Pudendal Channel Syndrome (Pudendal Nerve Trapping). It is a neuropathy of pudendal nerve with chronic pain in prostate, scrotum, and rectum. Pudendal neuropathy exists by compression of nerve in subluxation of the muscle levatore of anus. Clinical manifestation can accompany by fecal or urinary incontinence. Additionally, there exists hypoesthesia or anesthesia of the perineal area. Combined cases of orchialgia with proctalgia are reported that improved with the erecting position. When exploring surgically, it is found that pudendal nerve caught in the channel of Alcock in contact with sacroespinouse ligament. This condition is described specially in cyclists *(125–128)*.

Gluteal Fibrositis. It is a potential cause of referred naturopathic scrotal pain *(20)*.

Phantom Orchialgia. This presentation of chronic pain is secondary to radiculitis by irritation of nerve roots between T10 and L1 *(129)*.

Lumbosacral Radiculopathic Pain. Discal hernia produces paroxistic pain usually subacute and finally chronic *(130)*.

Koro-Like Syndrome. It is a psychiatric suffering with anxiety and fear to die accompanied with genital retraction. A variety of this syndrome is pronounced by intense episodic scrotal pain accompanied by panic attacks *(131)*.

Diabetic Neuropathy. Reports of CTP exist as neuropathy complications of the diabetes *(16,132)*.

Tension Myalgia of the Pelvic Floor. It is a condition often triggered by anxiety with habitual contraction of the pelvic musculature *(133)*.

Pharmacologic

Acute Pain

The mechanism of pharmacological pain is variable, can be a chemical epididymitis with visceral pain but in other cases pain also can be neuropathic. They reported testicular pain secondary to ingestion of following medicines:

Mazindol. It is imidazoisoindol tricyclic that behaves like amine sympathetic-comimetic (amphetamine like) stimulating the central nervous system. Its used as anorexigen *(134)*.

Amiodarone. It is an antiarrhythmic of group III. Actions: Uses dependent block of sodium channels (for high affinity inactivate channels); blocks potassium channels; weakly blocks calcium channels; causes non-competitive block of alpha and beta adrenergic receptors; and causes chemical epididymitis. Secondary testicular pain has been described in up to 11% of adult patients. *(42,135)*.

Desipramine. Is a tricyclic antidepressant (TCA) that inhibits the reuptake of norepinephrine. Desipramine is an activate metabolite of imipramine. It is used to treat depression, it produces special testicular pain post-coital and painful retraction during intercourse *(136)*.

Dimeglumina Gadopentato (Gadolinium). Is a chemical element in periodic table with symbol Gd and atomic number 64. Solutions of organic gadolinium are used as intravenous radiocontrast agents to enhance images in medical magnetic resonance imaging. Testicular pain has been described in the setting of rapid IV injection *(137)*.

Inipramine Withdrawal. Manifestation of testicular angina is reported by withdrawal of inipramine-like antidepressant *(16,138)*.

Chronic Pain

Continued use of the medicaments that produce acute inflammatory pictures in testes can culminate in criteria of chronic orchialgia. If a condition of this type persists, it might be due to the physicians disregard or due to the accurate valuation of risk-benefit in the provision of appropriate treatment *(18,113)*.

Miscellaneous

Acute pain

Among other causes of acute testicular pain with predominant visceral origin the following must also be considered:

Pelvic Congestion. It is present in adolescents without active sexual life that depends on the nocturnal pollutions to evacuate ejaculation or males with a low

coital frequency. Colloquially, it is known like "fiancé colic," nevertheless there exists variations described as "pain by sex" or "orchialgia by dance," where there can be factors conjugated that produce the pain as micro-traumas and sexual excitement not solved *(113)*.

Appendicitis. The initial manifestation could appear like an acute testicular pain in right side *(139)*.

Meconium Periorchitis or Meconium Vaginalitis. It is an entity in new born babies with perforation from the scrotum to gastro intestinal system. It is more a cause of mass rather than of pain. It has the possibility of conservative management when it is suspected, and it is adequately diagnosed *(140)*.

Urethral Obstruction (Referred Pain). Exists a group of causes of testicular pain secondary to urethral obstruction or congestion that produces a referred pain to the testicle when the nerve is irritated by intimate contact of urethra with the genito-femoral nerve at level of L4.

Urethral Stones. Urethra innervations in nephritic colic imply pain radiated to ipsilateral testes *(13,18,113,141)*.

Obstruction Uretero Pelvic. As well as in lithiasis, the patient can speak about ipsilateral orchialgia referred to, in past episodes of renal pain *(142)*.

Retrocaval Ureter. Obstruction on urethra produces referred pain to right testicle.

Retroperitoneal Fibrosis. It has been reported between 8 and 15% of testicular pain referred in patients with this pathology *(23,143)*.

Hydronefphrosis. Any of the hydronefphrosis causes can produce pain by at least two mechanisms: by the urethral obstruction with reflection to the scrotum or by obstruction of the spermatic veins that cause secondary varicocele *(42)*.

Constipation. The distended colon of feces, particularly in children, can produce testicular pain by compression to urethra *(144)*.

Chronic Pain

Inguinal and Femoral Hernias. Inguinal hernias are different in children and adults; in children there exists a lack of obliteration of the vaginal process and the pain is not so frequent while in adults there exists a solution of continuity in fascia, and intermittent pain is more common. Indirect inguinal hernias lateral or lower to epigastria artery and with displacement through inguinal channel constitute 80% of cases; when the content is incarcerated, clinical manifestation can be of an acute scrotum. The symptoms vary between no painful mass or painful swollen mass. It must be kept in mind that the content of hernia can vary between the omentum that is the most common, thin intestine, colon, and the rarest contents such as Meckel's diverticulum or urinary bladder. For diagnosis with ultrasound air presence of scrotal content can help *(42,113)*.

Retractile Testes. Patients with testicular pain, feel relief when testes are pulled toward scrotum. They have hyperactive cremaster and other anatomical variations helping the pain. The use of a mesh of some kind of material that blocks testicular excursion toward the inguinal region has been proposed as a solution *(145)*.

Hydrocele simple, communicant or of spermatic cord. Simple accumulation of liquid in vaginal process or in a cord segment is generally a painless condition. Similar situation happens with communicant hydrocele being defined as a condition in which there is variation of size related to the physical activity and in which the conduit peritoneum–vaginal is persistent.

Secondary orchialgia has been reported when there exists an underlying inflammation of testes or epididymis, or hydrocele tensioned, or when hydrocele has been complicated by conditions such as trauma, bleeding, or infection. An extreme condition that can cause persistent deaf pain is abdomino-scrotal hydrocele that implies such an accumulation of liquid that the mass surpasses the inguinal ring internal *(27,44,146,147)*.

Epididymal Cyst (Spermatoceles). It is defined as a movable mass of epididymis that contains nonviable semen; as a general rule, it is considered painless but in different jobs, it has been reported as chronic pain. Cysts are reported as cause of chronic pain, in some articles are even designated with the particular name of "epididymalgy." Usually, spermatoceles do not become infected but the increase of inflammatory substances like interleukin 6 (IL-6), interleukin (IL-8), and tumors necrosis factor alpha (TNF-a) in symptomatic cysts has been reported. The increase of these citoquines that could be involved in genesis of the cyst and in the pain would justify their surgical removal; however, the improvement of the pain with the simple aspiration of content of the cyst has been reported. In some cases, pain is so intense that it is a necessary resection of the cyst or even a epididymectomy. More severe complication appears when the patient presents "Dysplasia or cystic degeneration of testis," generally bilateral, with cysts in other organs as the kidney and whose diagnosis has been with ultrasound *(16,146,148)*.

Hyperuricemia. Deposit of uric acid crystal in the channels of epididymis is reported like cause of chronic orchialgia. In general, any cause that takes ecstasy of rete testes is a potential cause of chronic pain *(16,149)*.

Macro-orchidism. The increase of the testicular volume to more than 25 cc in adults is part of syndromes like the Atquín-Flaitz and Martin Bell. Mental retardation, usually comes along with Marfanoide habit and chromosomic alterations. In addition to alteration of the spermatogenesis in testes, the patients can show tumors, cystic degeneration, or testicular microlithiasis. It can be cause of chronic orchialgia *(150)*.

Testicular Microlithiasis. Having the vigorous scrutiny to this condition by its potential association to cancer of testes, a relation with testicle pain has been searched. The studies have determined that by itself microlithiasis is not pain cause, but rather infection or subacute torsion in this setting *(18,99,151,152)*.

Constrictive Albuginitis. In patients with chronic pain, a peritubular fibrosis with a heavy, yellowish, and rigid testicular albuginea showing an excess of hyalinosis can be found *(153)*.

Multiple Myeloma. The testicular presentation, generally bilateral, is rare but possible extramedullary manifestation of myeloma, which may require orchietomy as part of therapy *(154)*.

Sarcoidosis. This disease can infiltrate testes producing chronic pain *(18,155)*.

Abdominal Neoplasm. The testicular pain can be developed by secondary varicocele. If the tumor is in right side, the congestion testicular is only in the same side. In men older than 40 years with unilateral right varicocele, one must always suspect about an intra-abdominal or retroperitoneal tumor *(42)*.

Cirrhosis. The cirrhosis can cause testicular pain due to secondary varicocele *(42)*.

TREATMENT: GENERAL APPROACH

The treatment of the orchialgia can be divided in two major groups (Table 3):

Pharmacological Treatment Options

A very important therapeutic implication exists since the neuropathic pain is not relieved with common analgesic, it does not even yield to the use of opiate, and in

Table 3
Testicular Pain: Treatment Options

Pharmacologic treatment options
- Analgesics non-opioids
- Analgesics opioids
- Non-steroidal anti-inflammatory drugs
- Cannabinoid analgesia
- Antibiotics
- Anticonvulsivants
- Neuroleptics
- Tricyclic antidepressant
- Alpha-adrenergic antagonists
- Allopurinol

Non-pharmacologic treatment options

Non-invasive treatment options
- Restricted physical activity
- TENS (Trans-cutaneous electrical nerve stimulator)
- Pulsed radio frequency
- Psycotherapy
- Hypnosis

Minimal invasive treatment options
- Needle aspiration of cyst
- Local anaesthesic infiltration of the spermatic cord with or without steroids
- Local anaesthesic infiltration of the pelvic plexus under TRUS guidance
- Direct intra-prostatic injection of antibiotic or steroids
- Acupuncture

Surgical treatment options
- Denervation of the spermatic cord (Microscopic or laparoscopic)
- Denervation sympathetic of the spermatic cord
- Laparoscopic resection of spermatic cord
- Decompression of the pudendal nerve
- Vasovasostomy
- Vasoepidymostomy
- Sperm granuloma excision
- Varicocele ligation
- Hydrocelectomy
- Spermatocelectomy
- Orchidopexy
- Epididymectomy
- Orchidectomy

case of testes, it might not improve with such radical conduct as orchidectomy *(16, 19–25)*.

Analgesics Non-Opioids

They are first step of analgesic management. They include medicines as paracetamol or acetaminophen.

Analgesics Opioids

Opioids have been considered more useful in inflammatory problems than in neuropathic pain. The treatment with opiate medicines make a balance between risk and benefit by side effects in patient as tolerance, addiction, and physical dependence.

Non-Steroidal Anti-Inflammatory Drugs

They are an option as anti-inflammatory and analgesic.

Cannabinoid Analgesia

Cannabinoid receptors CB1 are located in area of the spinal cord associated with nociception and with regulation of the calcium flow. Medicines of this group will be useful in the handling of neuropathic pain *(24,156)*.

Antimicrobials

According to the site of infection and the isolated germ. The most common drugs suggested for initial therapy in acute prostatitis or epididymytis are one of the fluoroquinolones, second or third-generation cephalosporins, or aminoglycoside (i.e., amikacin) alone or in combination with penicillin. Once the acute infection has settled down, therapy should be continued with one of the oral antimicrobials appropriate for the treatment of chronic bacterial prostatitis (e.g., trimethoprim or fluoroquinolones). Optimal duration of therapy is unknown, it has been suggested between 2 and 6 weeks. The most commonly used antimicrobial agent in chronic prostatitis is trimethoprim-sulfamethoxazole. It seems that longer duration therapy (90 days) provides the best clinical results.

Anticonvulsivants

Gabapentin and carbamazepine have been useful to alleviate hyperalgesy and allodynia characteristic of neuropathic pain *(24)*.

Neuroleptics

Medicines of the type of chlorpromazine can be effective in the handling of the CTP.

Tricyclic Antidepressant

Medicines as amitriptyline have been used as complement in the handling of the chronic pain.

Alpha-Adrenergic Antagonists

Muscle peristaltic contraction induced by adrenergic neurotransmitters is important in propelling the duct contents. It has been advocated that the CTP in some patients

might be their functional obstruction/spasm along the length of the vas epididymis. It has been shown that human scrotal vas deferens has similar distribution of receptors to prostate smooth muscle, suggesting that the use of a selective a1 antagonist might relieve a possible obstruction/spasm of the vas deferens. Clinically, drugs that modify the activity of prostate smooth muscle should also affect the vas. Therefore, for patients who fail to respond to conservative management and wish to avoid the surgical options that are available in treating chronic orchialgia, a trial with α-adrenergic antagonist might be an option.

Allopurinol

For patients with diagnosis of hyperuricemia with testicular pain.

Non-Pharmacological Treatment Options

Non-Invasive Treatment Options

Physical Restricted Activity. It is a complementary option of treatment in special cases originated of pain in inflammatory acute pictures.

TENS (Trans-Cutaneous Electrical Nerve Stimulator). By electrical stimulation of some nervous fiber, it is the aim to block pain transmission at the central level. It has been used in back pain and could be an alternative in the testicular pain of radicular origin *(16)*.

Pulsed Radio Frequency. Improvement has been reported with the use of pulsed radio frequency of the nerves innervating these areas *(16,157)*.

Psychotherapy. Cognitive behavioral therapies can attenuate or improve cases of patients with CTP *(23,27)*.

Hypnosis. It is a therapeutic method very little used in urology but it could be used to improve of chronic pain *(27)*.

Minimal Invasive Treatment Options

Needle Aspiration of Cyst. It is a controversial therapeutic option for spermatic cysts of the cord *(16)*.

Local Anesthetic Infiltration of the Spermatic Cord with or Without Steroids. It can be preformed as definitive therapy when the patient gets well or as therapeutic test before denervating procedure *(16)*.

Local Anesthetic Infiltration of the Pelvic Plexus Under TRUS Guidance. The blockage of the periprostatic nerves with mixture of lidocaine and steroids can alleviate the testicular pain as pelvic plexus can be a way that provides sympathic and parasympathic innervation to the testicle even more than spermatic plexus *(13,16)*.

Direct Intra-Prostate Injection of Antibiotic, Anesthetic, or Steroids. It is a therapeutic option to access directly to pelvic plexus. A number of investigators have advocated direct injection of antibiotics into the prostate gland in cases of prostatitis classification III, but this method has never been rigorously evaluated or become popular among urologists *(16,158)*.

Acupuncture. Has been used by practitioners of traditional Chinese medicine to treat variety of illnesses for more than 2000 years. Different studies have shown that acupuncture may be effective in the treatment of various types of pain. The effects may be mediated by neuromodulation to inhibit transmission of pain, as well as to normalize the function of various midbrain nucleuses *(27,159)*.

Surgical Treatment Options

Denervation of the Spermatic Cord. There have been described the neurectomy of the nerves ilioinguinal, iliohypogastric, or genito-femoral to improve the chronic pain. The most common technique implies division of the ilioinguinal nerve and its branches. Two techniques have been reported: opened with the use of microscope and laparoscope. It is recommended to do it, after verifying that the blockade of the cord with anesthetic was effective as a transitory relief of the pain *(12,16,160,161)*.

Denervation Sympathetic of the Spermatic Cord. It is described in post-vasectomy syndrome as the exclusive eradication of the sympathetic innervations in the cord to eliminate sympathetic dystrophy reflex *(16)*.

Resection of Spermatic Cord. At least one case of solution of relief completes orchialgia that was achieved by laparoscopic resection of both spermatic cords after embolization of varicocele for CTP with Gianturco coils *(162)*.

Pudendal Decompression. Pudendal nerve trapped can be treated with decompression surgery to alleviate the pain *(122,123)*.

Vaso-Vasostomy and Vaso-Epidymostomy. It is a treatment for post-vasectomy orchialgia syndrome (PVOS) *(16,69,78)*.

Sperm Granuloma Excision. It is a treatment for PVOS *(16,78)*.

Varicocelectomy. Varicocele ligation can be an effective option for treatment of testicular pain originated in dilatation of pampiniform plexus. Surgical techniques used include high inguinal, subinguinal, laparoscopic, or embolización. Although the procedure can be in itself an orchialgia cause, numerous studies have confirmed the improvement of the testicular pain with the tie of varicocele *(163–165)*.

Hydrocelectomy. As a treatment of hydrocele causing testicular pain, inguinal and scrotal access can be done.

Inguinal Herniorrhaphy. For correction of inguinal hernias direct or indirect.

Spermatocelectomy. For treatment of spermatocele that is causing testicular pain.

Orchidopexy. As treatment of an ITT.

Epididymectomy. It is a procedure with contradictory results. It is used in persistent, chronic, post-vasectomy pain, with enlargement of epididymis. In patients with quite inflammatory histology, poor results can be anticipated. Nevertheless, it has been also used as treatment of the epididymitis pain *(16,27,77,78,166,167)*.

Orchiectomy. It is the last and final option of treatment. Unfortunately, a number of patients fail to respond to both conservative and less invasive treatment methods, and for them, the only available therapeutic option is orchiectomy. Scrotal access (improvement of pain in 55%) or inguinal access (improvement of pain in 73%) can be made *(16,21,27)*.

CONCLUSION

Testicular pain is a vast field where multiple organs and systems convey together. Urologist should go through it equipped with a powerful arsenal diagnosis, with an open mind and full of a healthy skepticism that allows him avoid the common places in his clinical judgment.

To understand the testicular chronic pain as part of "complex painful syndrome" with an enigmatic origin, a specific biochemical cascade, amazing symptoms and a treatment where the common analgesic fail and even the opiate ones, will allow the urologist to tune himself better with the onset that the patient presents to him.

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11 Bacterial Prostatitis

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Summary

Bacterial prostatitis includes: acute bacterial prostatitis (ABP) and chronic bacterial prostatitis (CBP). Most infections involve only a single bacterial organism. ABP generally presents as a severe febrile illness. CBP is characterized by recurrent urinary tract infection (UTI) due to the same organism, which persists in the prostatic fluid. This chapter outlines the etiologies, diagnosis, evaluation, and treatment of both acute and CBP.

Key Words: Acute bacterial prostatitis; chronic bacterial prostatitis; urinary tract infection; prostatic abscess; antimicrobial therapy.

Contents

INTRODUCTION

Prostatitis is considered an inflammation of the prostate gland, which can be infectious (i.e., bacterial prostatitis) or noninfectious (i.e., chronic pelvic pain syndrome) in origin. Bacterial prostatitis is further divided into acute (ABP) and chronic (CBP) form. ABP presents as a severe, febrile illness. CBP presents as recurrent urinary tract infections (UTI) with the same bacterial strain, and a chronic infection of the prostate due to the same organism.

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INCIDENCE

How common is bacterial prostatitis? There have been few good studies on the prevalence of bacterial prostatitis *(1)*. Together, the two forms of bacterial prostatitis comprise less than 10% of all prostatitis syndromes *(2)*. Another recent study performed in a managed care setting estimates the incidence of ABP and CBP as 102,000 cases per year in the USA or about 0.33% *(3)*.

ETIOLOGY/PATHOGENESIS

UTI plays a central role in the pathogenesis of ABP and CBP. Important questions to consider are whether normal prostates are colonized with bacteria and whether the presence of bacteria correlates with the presence of prostatic inflammation.

Duncan et al. showed that there are no bacteria present in the normal prostate of healthy cadaveric organ donors. However, there are bacteria, as detected by a sensitive PCR assay, present in the prostates of patients with concurrent histological evidence of prostatic inflammation *(4)*. Thus, bacterial colonization of the prostate is probably pathologic.

Leading theory suggests that in ABP, the bacteria ascend to infect the prostate *(5)*. In CBP, the bacteria colonize the prostate, which then serves as a nidus for recurrent UTI *(6)*.

Bacterial colonization is facilitated by:

- Ascending urethral infection: Ascending urethral infection may occur following sexual intercourse. Inoculation may occur during cystoscopy, other instrumentation, prolonged catheterization, or unprotected anal intercourse.
- Intraprostatic urinary reflux: Infected urine refluxes into the ejaculatory and prostatic ducts that empty into the posterior urethra. Urine reflux also may occur in urethral stricture disease. Because of the anatomy of the prostate gland, ducts that drain glands in the peripheral zone are positioned more horizontally than other prostatic ducts and, thus, facilitate the reflux of urine into the prostate. Consequently, most infections occur in the peripheral zone. Refluxing urine, even when sterile, may cause chemical irritation and initiate tubule fibrosis and prostatic stone formation, which then lead to intraductal obstruction and stagnation of intraductal secretions. Bacterial colonies can serve as a nidus for relapsing infections.
- Direct invasion or lymphogenous spread from the rectum, which may be facilitated by injury to the rectal wall by constipation or trauma (i.e., prostate biopsy).
- Direct hematogenous infection.

Most infections involve only a single bacterial organism. Occasionally, two or three strains of bacteria may be involved. The organisms primarily responsible for bacterial prostatitis are also those responsible for most UTI *(7)*: *Escherichia coli* (about 80%), *Klebsiella* species, *Pseudomonas aeruginosa*, and *Enterococcus faecalis*. Nosocomial strains of bacteria are often cultured from the prostates of men with CBP or ABP after hospitalization and genitourinary manipulation *(8)*.

ABP

Clinical Presentation

ABP presents dramatically with sepsis including moderate-to-high fever and chills and generalized malaise, possibly with arthralgia and myalgia. Symptoms from the prostatic inflammation include low back and perineal pain. The associated prostatic swelling, cystitis, and urethritis cause urinary frequency and urgency, nocturia, and dysuria.

ABP may result in acute urinary retention from inflammation-induced bladder outlet obstruction.

Differential Diagnosis

- Acute pyelonephritis: lacks the prostatic tenderness, edema, and firmness.
- Fever of unknown origin: ABP should be in the differential diagnosis of an obtunded, bedridden patient with a prolonged urethral catheterization with persistent fever or sepsis.
- Urogenital infection: can cause perineal pain and dysuria.

Evaluation

The essential elements of an evaluation for ABP include a history, physical examination with gentle prostate exam, urinalysis, and urine culture. History should focus on obstructive symptoms such as hesitancy, weak urinary stream, double voiding, and sensation of incomplete emptying. Additionally, elicit a history of recent urologic instrumentation or prostate biopsy, immunocompromised status, and previous episodes.

On physical exam, digital rectal exam usually reveals an enlarged, exquisitely tender, edematous prostate gland, which is firm, warm, and occasionally, irregular to the touch. Care must be taken to avoid vigorous prostatic massage in a patient with suspected ABP to avoid bacteremia and sepsis *(9)*. A urinalysis will show evidence of an acute cystitis and a urine culture will be positive.

Fever of unknown origin in nonresponsive patients can make diagnosing ABP difficult. Given the lack of elicited classic physical exam findings and symptomatology, further evaluation may be needed to secure the diagnosis. While the literature does not provide sufficient evidence to validate their use, ^{111}indium-labeled leukocyte studies and serum prostate specific antigen (PSA), while not usually indicated, can aid in the diagnosis of ABP in equivocal cases.

Specifically, a ^{111}indium-labeled leukocyte study can be useful in differentiating UTI without prostatitis from ABP *(10)*. In a small prospective trial, the radiolabeled leukocytes were shown to accumulate in the prostates of subjects with ABP but not in those with UTI without evidence of prostatitis. Additionally, PSA levels have been shown to be elevated in ABP and significantly fall after treatment with antimicrobial therapy *(11)*.

Management

The first decision hinges on deciding whether the patient should be hospitalized or given an outpatient antimicrobial regimen. If the patient has frank sepsis, urinary retention, or personal circumstances making adherence to an outpatient course of treatment unlikely, then the patient should be hospitalized and administered parenteral antimicrobials*(12)*. If there is frank sepsis, blood cultures should be obtained.

If there is evidence of ineffective voiding, one can attempt gentle passage of a small Foley catheter. If unsuccessful, rather than attempting a more vigorous placement or placing a larger Foley catheter, suprapubic catheterization can be performed to avoid seeding the bloodstream with prostatic uropathogens *(13,14)*.

As compared to CBP, the acutely inflamed prostate can be easily penetrated by antimicrobials. For inpatients, efficacious parenteral antimicrobial regimen includes an aminoglycoside paired with ampicillin or broad-spectrum penicillin with a beta-lactamase inhibitor, a third generation cephalosporin or a fluoroquinolone, which are administered until urosepsis resolves and the patient defervesce *(15)*.

Either following the abatement of systemic symptoms or in the clinically well-appearing patient, outpatient therapy with 4–6 weeks of an oral fluoroquinolone *(16)*, or trimethoprim–sulfamethoxazole (TMP–SMZ) is reasonable *(13,17)*.

If the initial response to medical therapy is favorable, then patient prognosis is very good. However, follow-up should include a repeat urine culture after completion of antimicrobial therapy to ensure that infection is no longer present. If the patient fails to respond fully to therapy, or quickly relapses and has ongoing symptoms, the diagnosis of a prostatic abscess should be considered *(13)*. The common risk factors include immunocompromised status, diabetes mellitus, previous urethral instrumentation or prolonged use of indwelling urethral catheters, and renal transplantation. A fluctuant mass is felt in the prostate gland *(13)*. This can be confirmed by transrectal ultrasound, CT, or MRI *(9)*. Coliform bacteria, especially *E. coli*, cause more than 70% of prostatic abscesses, but anaerobes may also be involved. Once an abscess is diagnosed, anaerobic antimicrobial therapy should be added to the treatment regimen. Clindamycin intravenously at 600–900 mg q8h or orally at 150–450 mg q8h is a good choice. However, medical management often is not successful. Transrectal or perineal aspiration of the abscess is preferred and often is effective, especially if symptoms do not improve after 1 week of medical therapy. Transurethral resection of the prostate (TURP) and drainage of the cavity is another approach *(13)*. TURP in the setting of prostatitis has a high association with urinary incontinence and should be reserved for refractory cases. Recurrent abscesses are rare.

Related Evaluations

Patients with ABP may have associated issues that warrant further evaluation by an urologist after the resolution of the ABP episode. Prostatitis represents a complicated UTI in a male. Therefore, the urologist will have to evaluate the upper and lower urinary tracts for correctable causes of UTI. The patient will need upper tract imaging (e.g., CT, MRI, intravenous pyelogram, or ultrasound) and cystoscopy *(14)*.

If a serum PSA is obtained in an equivocal case and found to be elevated during the course of ABP, measure another PSA 3–6 months after completion of therapy when the patient becomes asymptomatic and has a negative urine culture. If an elevated PSA persists, the patient should be evaluated for possible prostate cancer.

CBP

Clinical Presentations

Most patients who think they have CBP actually have the prostatitis symptom complex, which is very common and typically presents with symptoms of chronic

pelvic pain with intermittent irritative or obstructive urologic symptoms. Patients with CBP can be differentiated from those with prostatitis by documentation of recurrent UTIs *(18)*.

Differential Diagnosis

Other clinical entities that should be considered in the differential diagnosis include chronic nonbacterial prostatitis/chronic pelvic pain syndrome, urethral stricture, urethritis, anatomic obstruction due to prostatic hyperplasia, urinary stricture disease or bladder neck dysfunction, and colorectal disease such as diverticulitis.

Evaluation

History, physical examination with attention to the genitourinary system, urine culture, and microscopic analysis is the starting point of CBP evaluation. It is essential to document a history of recurrent UTIs. If possible, urine culture records should be obtained. If no positive cultures are available, then urine culture should be repeated during future episodes when the "cystitis" symptoms are present. If the studies are not consistent with prostate infection, then initiate a urologic evaluation for recurrent cystitis. If they remain negative, then the patient should undergo evaluation for chronic pelvic pain syndrome/chronic nonbacterial prostatitis and other causes of lower urinary tract symptoms. If the urine cultures are positive, repeated, and show the same strain, localization urine cultures should be performed to elucidate the presence of bacterial infection and inflammation in the prostate. The criterion standard localization culture is the Meares–Stamey four-glass test *(19)*. This involves collecting serial urine samples in a well-hydrated patient. The process is as follows:

- The first 10 mL of voided urine represents urethral flora and possible inflammation (VB1).
- A midstream sample after 200 mL has been voided represents bladder flora and possible inflammation (VB2).
- The expressed prostatic secretions (EPS) are collected after prostatic massage. They represent prostate flora and possible inflammation.
- The 10 mL voided urine sample (post-massage) represents diluted prostatic flora and inflammation (VB3).

After careful labeling, the four urine specimens should be sent for microscopic analysis and culture. The microscopic evaluation should identify white blood cells per high power field.

Management

If the VB1 and VB2 urine cultures are negative and a log or more growth of a uropathogen is identified in the EPS or VB3 sample, then the patient has CBP. Intraprostatic urinary reflux is thought to initiate prostatic infection in the poorly draining tissue *(13)*. In CBP, the infection often persists because antimicrobials do not penetrate the chronically infected prostate easily. Antimicrobials depend on passive diffusion to enter the epithelial-lined prostatic glandular acini. The epithelial cells do not allow the free passage of antimicrobials unless they meet certain criteria; that is, un-ionized, lipid-soluble, and not firmly protein-bound *(18)*. Fluoroquinolones and

TMP meet these criteria. The patient should be treated with fluoroquinolones based on their antimicrobial susceptibility for 4–6 weeks.

Difficulties With Management

In most cases, appropriate antimicrobial therapy will successfully clear the infection and resolve the symptoms. Treatment success rates with TMP–SMZ approach 30–40% and success rates with fluoroquinolones are 60–90%. In a recent study by Weidner et al., 40 men diagnosed with CBP were treated with ciprofloxacin for 4 weeks. Bacterial sterilization of the EPS was found in 92% of patients examined at 3 months and in 80% of patients examined at 24 months *(20)*. There are times when the symptoms persist after appropriate antimicrobial therapy despite obtaining a negative urine culture, indicating eradication of the infection. These patients should be considered to have chronic pelvic pain syndrome *(21)*.

If antimicrobial therapy does not eradicate the prostatic bacteria, then one can consider several options: intermittent treatment of cystitis, long-term suppressive antimicrobial therapy, or resection of infective prostate tissue by transurethral resection or open prostatectomy. Suppressive antimicrobial therapy consists of a low dose of antimicrobials such as TMP-SMZ at single strength qhs, TMP at 100 mg qhs, ciprofloxacin at 250 mg qhs, and ofloxacin at 200 mg qhs *(22,23)*. Intraprostatic injection of antimicrobials is under investigation for treatment-refractory CBP *(24)*. Surgery usually is not indicated for CBP. However, in select situations when a patient has recurrent episodes of CBP and improves with antimicrobials, a TURP may remove a nidus of infection. The nidus may be prostatic stones, which can often be visualized with transrectal ultrasound *(25)*. Surgical resection of the prostate is associated with urinary incontinence and is considered a last resort *(26)*.

The "infection" should be treated with an antimicrobial that does not penetrate the prostate such as nitrofurantoin or a beta lactam so that Meares–Stamey localization cultures can be performed to aid in the diagnosis of CBP *(8)*.

The addition of nonsteroidal antiinflammatory drugs and alpha blockers (e.g., terazosin at 1–10 mg and doxazosin at 1–8 mg) may help with symptom relief. They can help decrease recurrences by diminishing urinary obstruction due to prostate enlargement or congestion secondary to inflammation *(27)*.

Related Evaluation

The lower urinary tract symptom complex of CBP can include bladder outlet obstruction and can be mimicked by other causes of bladder outlet obstruction (e.g., BPH and urethral stricture). If the patient suspected of having prostatitis has obstructive voiding complaints or evidence of urinary retention, flow rate recordings can be added to the initial evaluation by an urologist. A low maximum flow rate may indicate bladder outlet obstruction due to prostatitis. If this improves during or after treatment, then serial flow rate measurements provide a measure of the response to treatments. However, a low flow rate can be seen in a poorly contractile bladder. A low maximum urinary flow rate raises concern for impending acute urinary retention, which predisposes to worsening of urogenital infections and acute renal failure. Post-void residuals using transabdominal ultrasonography should be measured to avoid these outcomes.

A low maximum urinary flow rate is equivocal at best because this is seen in both bladder outlet obstruction and detrusor hypoactivity. Bladder outlet obstruction can

be addressed with surgeries or treatments. On the other hand, therapies for detrusor hypocontractility, including anticholinergics and biofeedback, are aimed at the underlying disease processes and focus on symptom relief. Pressure-flow urodynamic testing aids in differentiating outlet obstruction from detrusor hypocontractility. The best piece of information from the urodynamics study to discern obstruction from poor bladder contractility is the detrusor pressure at the time of the maximum urinary flow rate *(21)*.

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12 Chronic Prostatitis/Chronic Pelvic Pain Syndrome

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SUMMARY

The past 5 years have seen exponential growth in etiologic research and evidence-based therapies for chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). The focus of this chapter is on symptomatic men without urinary tract infection (UTI), those classified as CPPS or NIH category III. The authors cover etiologies, diagnosis, evaluation, and treatments, including antimicrobials, anti-inflammatory agents, alpha blockers, hormonal manipulations, prostate massage and ejaculation, surgery and minimally invasive therapy, and alternative medicine.

KEY WORDS: Chronic prostatitis; chronic pelvic pain syndrome; bacterial prostatitis; prostate; urinary tract infection; alternative medicine; evidence-based medicine.

CONTENTS

INTRODUCTION

Few conditions in urology are as prevalent and yet as enigmatic as chronic prostatitis (CP). For decades, the condition has been long on hypotheses and short on data. The past 5 years, however, has seen exponential growth in etiologic research and

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evidence-based therapies. In this chapter, we will review the latest developments in our understanding of the CP syndromes as well as practical, evidence-based advice for the management of these challenging patients. Our focus will be on symptomatic men without urinary tract infection (UTI), those now classified as chronic pelvic pain syndrome (CPPS) or NIH category III.

CLASSIFICATION

One of the earliest attempts at a classification system for CP was made in 1978 by Drach et al. *(1)* and is presented in Table 1. This classification system was based on patient symptoms and localizing bacterial cultures published by Meares and Stamey 10 years before *(2)*. The "four-glass test" localization study collected first-voided urine (VB1), mid-stream urine (VB2), prostatic fluid [expressed prostatic secretions (EPS)], and post-prostate massage urine (VB3) and subjected each to microscopic WBC count and EPS. It is important to emphasize that this four-glass test was designed only to help localize the source of a male UTI, not to diagnose the cause of pelvic pain. Drach et al. proposed the use of this localization test as a way to classify prostatitis. It is now referred to as the traditional classification system of prostatitis. Acute bacterial prostatitis was defined as an acute febrile UTI. The chronic bacterial prostatitis was defined as recurrent UTI in which bacteria and WBCs were found in the EPS at levels significantly higher than any found in the pre-massage urine. The diagnosis of non-bacterial prostatitis was defined as WBCs but not bacteria in EPS or VB3. Finally, prostatodynia was used to refer to patients with typical symptoms but without any WBCs or bacteria recovered from prostatic secretions. Unfortunately, this classification

Table 1
Classification of Prostatitis

Traditional	NIH	Description
Acute bacterial prostatitis	Cat. I	Acute bacterial infection of the parenchyma of the prostate
Chronic bacterial prostatitis	Cat. II	Chronic infection of the prostate gland
Not applicable	Cat. III/CPPS	Chronic GU pain. No pathogenic microorganisms localized to the prostate by standard methods
Nonbacterial prostatitis	Cat. IIIA	Significant number of WBCs present in semen, post-prostatic massage secretion, or expressed prostatic secretions
Prostatodynia	Cat. IIIB	No significant number of WBCs present in semen, post-prostatic massage secretion, or expressed prostatic secretions
Not applicable	Cat. IV	WBCs/bacteria present in semen, post-prostatic massage secretion, expressed prostatic secretions, or histologic specimens of prostate in the absence of symptoms

system was never formally validated and seldom used by most physicians *(3,4)*. Indeed, there is still no evidence that men with traditional chronic bacterial prostatitis versus non-bacterial prostatitis respond differently to therapy. Recognizing this, a simpler, two-glass test originally described by Weidner et al. *(5)* was popularized by Nickel as an adequate replacement to the more cumbersome four-glass test *(6)*. In the two-glass test, only pre-and post-prostate massage urine is examined and cultured.

Recognizing the shortcomings of the current classification system, together with the lack of consensus for treatment and the importance of this health problem, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) began an initiative to address prostatitis in 1995. The NIH classification system, which is presented together with the traditional system in Table 1, was ultimately published in 1999 *(7)*. Given our lack of understanding of the basic etiology of CP/CPPS, the original, etiology-driven classification system was replaced by a symptom/syndrome-driven classification. Categories I and II are identical to the acute bacterial and the chronic bacterial prostatitis of the previous classification system. Category III/CPPS is defined as the presence of genitourinary pain in the absence of uropathogenic bacteria detected by standard microbiological methods. Very importantly, the new definition recognizes that pain is the main symptom of non-bacterial prostatitis. Category III was further divided into categories IIIA and IIIB. Category IIIA represents inflammatory CPPS where WBCs can be found in semen, expressed prostatic secretions (EPS), or urine after prostatic massage. In category IIIB (non-inflammatory CPPS), no such cells can be demonstrated. The actual cutoff points to differentiate IIIA from IIIB by number of WBCs have never been determined. In category IV or asymptomatic inflammatory prostatitis no subjective symptoms of pain can be demonstrated, but WBCs can be found in prostate secretions or in prostate tissue during an evaluation for other disorders (infertility, BPH, or prostate cancer). The new classification system has been validated for both research and clinical practice *(8)*.

EPIDEMIOLOGY

Valuable insights into the etiology of a disease can often be gained from epidemiological data. There is unfortunately scant epidemiological literature concerning CP/CPPS. The previous classification of prostatitis was not widely used by clinicians *(3)*, and any epidemiology was symptom or coding based.

While not a true epidemiologic study, the NIH-funded CP cohort (CPC) study provided the most descriptive longitudinal data on CP/CPPS to date *(9)*. In this important study, 488 participants with symptoms related to CP/CPPS and 120 asymptomatic controls were recruited. Average age was 42.8 (range 20–83), with a mean duration of the prostatitis symptoms for 6.9 years. The majority were white, educated beyond high school, earning more than 50,000 USD per year, and were living with a partner. This study also shed light on the significant impact on life quality associated with CP/CPPS. Indeed, 20% of the patients reported voiding three times or more nightly while 11% of the patients voided more than 15 times per 24-h period. Pain at multiple locations was also a central symptom, with 68% of the patients reporting pain between the rectum and the testicles. Objectively, the highest prevalence of tenderness during physical examination was in the prostatic region in 38% of the patients. Various medical conditions were also present in a number of patients, with genitourinary condition being present in 55% of patients and allergies present in 53%. Also, a third of these

patients had a history of urological surgery (self-reported). A significant proportion of patients (54%) had undergone cystoscopy. Antimicrobial use was reported by 95% of those patients and 66% reported the use of anti-inflammatory agents. Interestingly, 55% of patients reported the use of plant extracts or herbs. A selection bias may have been present from the very design of this study as most of the patients were recruited from the urological practices of the investigators and may therefore be representative of a tertiary center urological practice.

By its very design, the CPC did not provide any prevalence or incidence of CP/CPPS. A number of quality epidemiological studies are available based on North American population. Only one study, however, used the NIH-CPSI to study the epidemiology of CP/CPPS in the community *(10)*. Even though the NIH-CPSI was not designed to diagnose CP/CPPS, but rather to follow the natural history of the disease and response to treatment *(10)*, it comes closest to a discriminative tool until one is expressly designed for that purpose.

The study by Nickel et al. *(10)* is a cross-sectional survey of the prevalence of prostatitis-like symptoms in men between 20 and 74 years of age in eastern Canada. Average age of their 868 patients was 52.1 ± 13.5. Using the NIH-CPSI, it was found that 9.7% of their patients presented CP-like symptoms. Most of their patients were younger than 50 years old. Similarly to the study by Shaefer et al. *(11)*, genitourinary-perineal pain was a common complaint. As common in postal studies, there may be a response bias in their study. Indeed, their response rate was low (30%), and it may be that men with CPPS are more likely to respond to such a solicitation that men without. Similarly, younger people are underrepresented in their and in most postal studies.

Another group used questions similar to the NIH-CPSI to study in a population of older men in Olmsted County, Minnesota *(12)*. Among 1541 men aged 40–79, it was found that 2.2% reported CP-like symptoms. Collins and co-workers used the US National Ambulatory Medical Care Survey database to analyze 58,955 outpatient physician visits by men 18 or older *(13)*. Prostatitis was diagnosed in 8% of all visits to a urologist and 1% of all visits to a primary care physician. In their study population, prostatitis was more likely to be diagnosed in patients 36–65 years old than in younger patients. In this type of study, prevalence or incidence cannot be calculated. However, studies such as this one can provide us with an estimate of the importance of CP/CPPS as a health issue. The same group reported on the epidemiology of CP/CPPS among 31,681 US health professionals without prostate cancer *(14)*. The prevalence of a self-reported history of prostatitis was 16%. Men reporting a history of BPH had greater (7.7×) odds of a history of prostatitis, as did those of with LUTS (1.8–2.8×). Stress (1.2–1.5×) and a history of sexually transmitted disease were also found to increase the risk of CP/CPPS. Another study by Moon et al., this time with younger man (20–49), found that 5% had a history of prostatitis *(15)*. Their study was based on 184 men from the Wisconsin National Guard.

It thus appears that, in North America at least, CP/CPPS is a significant health problem. Prevalence appears between 2 and 16% depending on the population studied, the epidemiological method, and the definitions of prostatitis. This underlines a significant burden on the health system in which prostatitis is a diagnosis in 2 million physician visits annually *(16)*. It is a significant health problem, responsible for more physician visit than BPH or prostate cancer in the USA *(17–19)*. Furthermore, its financial impact is not negligible, estimated at 4397 USD per year per person *(20)*.

CP/CPPS is a worldwide problem. A group in Korea, using the NIH-CPSI, reported a 6% incidence of CP/CPPS in men over 20 years of age *(21,22)*. Another study also using the NIH-CPSI comes from Malaysia. Using a localized, validated version of the NIH-CPSI *(23)*, they assessed the prevalence of CP/CPPS in a population of men aged 20–50 years *(24)*. Among 3147 men, they found that 275 (8.7%) were diagnosed with CP/CPPS. In their population, prevalence increased with age: 20–30 years 6.3%; 31–40 years 8.9%; and 41–50 years 12.6%. Interestingly, in the racially diverse Malaysia, there appears to be racial differences in the prevalence of prostatitis. Data will likely also be available from Japan, as a group recently localized and validated a Japanese version of the NIH-CPSI *(25)*. A group from Singapore performed a population-based study of prostatitis-like symptoms *(26)*. In their paper, respondents with pain or discomfort in the genitourinary/perineal area were classified as having prostatitis-like symptoms. Using their criteria, 29/1087 (2.7%) of men aged 21–70 had symptoms suggestive of CP/CPPS. Also using a postal questionnaire, a group from Finland performed a population-based cross-sectional survey *(27)*. Using their own questionnaire, they reported an incidence of prostatitis of 37.8/10000 person-year. There is also a localized and validated Italian version of the NIH-CPSI *(28)*, and it has been reported that prostatitis represented 12.8% of all urology outpatients in Italy, again emphasizing the important burden of prostatitis on health care *(29,30)*.

It is therefore evident that CP/CPPS is a worldwide health concern. Also, prevalence from studies outside North America (2.7–8.9%) is similar to the incidence found in North American studies (2–16%). These studies raise the interesting question of racial difference in CP/CPPS. Such differences could be genetic or environmental, and migration studies could answer such a question. It is also evident that further epidemiological studies should use the NIH-CPSI to standardize and to facilitate comparisons between studies.

DIAGNOSIS

Clinical Presentation

Pain is the most common symptom of CPPS. Patients will frequently report pain in the pelvic, suprapubic, or perineal area and also in the penis, frequently at the tip. Less frequently, pain can be localized in the testicles, inguinal area, or low back *(31,32)*. Pain on ejaculation may also be present and can sometimes be the only symptom of prostatitis and may indicate a worse prognosis *(33)*. Sexual dysfunction (pre-mature ejaculation and erectile dysfunction), although not used in the definition of CP/CPPS, appears very prevalent in this population *(34,35)*. There is some evidence that premature ejaculation and CP/CPPS may be linked *(36)*. Voiding symptoms, whether irritative or obstructive, are also central to the clinical syndrome *(29,31,37,38)*. The natural history of CP/CPPS is poorly described, but patients will typically report that symptoms wax and wane over time *(39)*. Most patients will report that their quality of life is impaired, with quality of life scores similar to patients with severe diabetes or Crohn's disease *(40–42)*.

Recommendations for the Evaluation

The following recommendations for the evaluation of a patient presenting with prostatitis are derived from recent international and North American consensus meetings *(43–46)*.

Basic Investigations

Evaluation of any patient begins with a thorough history. Present and past illnesses together with family history should be obtained. Previous surgeries with special attention to genitourinary procedures must be reviewed, and if possible, operating notes or result of cystoscopy should be obtained. The sexual history of the patient, together with previous sexually transmitted diseases or urethritis and sexual dysfunction can be important. A focused history should then explore the main complaints of the patient. The CPSI is a useful tool to quantify the degree and type of pain, LUTS, and quality of life impact. The physical examination should include the penis, scrotum, perineum, peri-anal and inguinal areas. A careful DRE should be performed to assess the prostate: size, consistency, irregularity, and tenderness. During the rectal examination, the internal pelvic muscles should be palpated to assess areas of muscle spasm or tenderness. Often patients will state that their symptoms are completely reproduced by palpating such a muscular "trigger point" which may be far from the prostate. Urine analysis and culture (mid-stream) should also be performed. Hematuria should not be attributed to the prostatitis but should be evaluated as in other patients without pelvic pain.

Recommended Investigations

Most prostatitis researchers perform further investigations, but their utility in a general non-research practice is yet unproven. A debate surrounds the use of lower urinary tract localization tests, the Stamey four-glass test, or the simpler pre/post-massage (two-glass test) originally described by Weidner et al. *(5)* and popularized by Nickel *(6)*. Aside from the fact that very few urologists perform these tests *(3,4)*, leukocyte and bacterial counts do not correlate with severity of symptoms *(47)*, do not characterize well each patient population *(48)*, and do not affect treatment outcome *(49)*.

Many experts include a flow rate and residual urine determination in their investigation of these patients. Indeed, flow rate suspicious of obstruction or elevated post-void residual volume may indicate other bladder or prostate pathology. Patients who present with irritative symptoms or hematuria should have a urine cytology. It has been reported that a minority of patients who present with symptoms suggestive of CP/CPPS may have carcinoma in situ of the bladder, especially if associated with hematuria *(50)*.

Optional Investigations

Urethral swabs (gonorrhea, chlamydia, and mycoplasma) may be warranted in selected patients with a history of unprotected sex or if urethral discharge is present. Urodynamics, while not routinely necessary, may help clarify complex voiding problems *(51–54)*. Cystoscopy is confined to regular indications (hematuria, suspicion of BPH, or stricture) but is not routinely necessary in CPPS. Imaging of the pelvis (pelvic US, CT scan, and MRI) similarly is used to rule out other conditions. MRI probably has the potential to demonstrate the most pathological conditions of the prostate including CP/CPPS *(55–57)*, but cannot "rule in" a diagnosis of CPPS. TRUS has been used to evaluate patients with CP/CPPS, but no obvious differences between CP/CPPS patients and controls could be found *(58)* even though it can sometimes identify a readily correctable pathology *(59)*. Young men with prostatic calcifications/stones may be amenable to novel therapies (see below). Finally, serum

prostate-specific antigen (PSA) should be treated no differently than for the patient without a diagnosis of CP/CPPS. PSA can be significantly elevated in category I and II prostatitis *(60)*, and it has been shown that treatment of category II prostatitis will lower PSA *(61,62)*.

ETIOLOGY

Infection

While the etiology of acute prostatitis is clearly a bacterial UTI, the etiology of CP/CPPS is far less clear *(63)*. Central to the controversy is whether the underlying cause is bacterial, autoimmune, or a form of neuro-muscular dysregulation. Historically, micro-organisms were most commonly implicated; however, uropathogens localized to the prostate are present in fewer than 10% of patients suffering from CP/CPPS *(64–66)*.

Gram-Negative Bacteria

The Enterobacteriaceae are responsible for most cases of chronic bacterial prostatitis. *Escherichia coli* alone is responsible for 65–80% of infections *(67)*, and Pseudomonas aeruginosa, Serratia sp, Klebsiella sp, and Enterobacter aerogenes account for 10–15% of cases *(68)*. It was therefore intuitive that the same family of bacteria could be involved in CP/CPPS, either directly, through sub-clinical infection, or as an initiating event. Interestingly, a murine model of *E. coli*-induced CP exists, but is of unclear practical relevance *(69)*.

As previously stated, uropathogens localized to the prostate have been found in fewer than 10% of patients with CP/CPPS *(64)*. However, it may be that the techniques employed are not adequate. Addressing the sensitivity issues with nested PCR, it has been reported that a group of patients with CP/CPPS harbored a wide range of 16S ribosomal DNA within their prostate *(70,71)*; however, a control group was lacking. In another study, evidence of DNA encoding ribosomal RNA was found in the prostate of 46% of patients suffering from CP/CPPS, but only in 20% of patients suffering from prostate carcinoma *(72)*. The same DNA sequences are not typically found in the prostates of organ donor patients *(73)*. Another group did not reach the same conclusions, however, and found the bacterial DNA in both patient groups *(74)*. It is likely that the determination of commensal from virulent organisms, the focal nature of prostatitis, and various techniques of bacterial protection (biofilm or prostatic calculi) will continue to impede evaluation of molecular results. This initial approach was somewhat crude, in that the primers used for PCR were not bacterium species specific. Also, the technique of nested PCR is highly sensitive, and contamination from other sources is always an issue *(75)*. It is unknown how long 16S DNA persist in the prostate after viable bacteria are gone. Further studies are likely to shed light on these puzzling observations *(76)*.

The hallmark of the presence of Enterobacteriacea is lipopolysaccharide (LPS) or endotoxin. It is a large, complex molecule with a wide range of effects on mammalian physiology and on the immune system more specifically (reviewed in *(77)*). LPS has been isolated in the prostatic secretions of patients with category III prostatitis, but not in control patients *(78)*. Again emphasizing the inadequate sensitivity of standard bacteriological cultures, those patients with LPS in their prostatic secretions had negative prostatic secretions culture. Another group also reported that level of LPS were higher in patients with category IIIA than in category IIIB and that those patients in category

IIIB had level no different from control patients *(79)*. Similar to the data on 16S DNA, it is unknown at this point how long do LPS persist in prostatic tissue after the micro-organism has been eliminated.

Gram-Positive Bacteria

The role of Gram-Positive micro-organisms in CP/CPPS is also controversial. Among gram-positive bacteria, Enterococcus is believed to account for 5–10% of documented prostate infections *(68)* and the gram-positive bacteria most readily accepted as a true uropathogen. Another confounding factor is that some of these organisms can be harmless commensals of the anterior urethra *(80,81)*.

Among other gram-positive bacteria, the data is less clear. Some groups isolated gram-positive micro-organisms, but not repeatedly *(82)*, whereas other groups have found the association more compelling *(83–85)*. The bacteria most commonly isolated include the staphylococcus and the enterococcus genera *(65,65,86)*. Early data also suggested that gram-positive colonization of the prostate somehow caused a local down-regulation of the immune system in the prostate, paving the way for colonization by other micro-organisms *(87)*. Expanded on the finding of 16S DNA previously presented, another group has reported that bacterium belonging to the genera Corynebacterium, some as yet unclassified, and other gram-positive bacteria are overrepresented in patients with CP/CPPS as compared to controls *(88)*. Furthermore, some of these organisms are fastidious and are difficult to culture.

Chlamydia

Chlamydia is another organism difficult to culture that may be implicated in CP/CPPS. Whereas a number of independent groups around the world could isolate *Chlamydia trachomatis* by culture *(89–91)*, PCR *(92,93)*, or in situ hybridization *(94)* in a small but significant proportion of patients with CP/CPPS, the finding is not universal *(95–97)*. Interestingly, most of the studies not reporting *C. trachomatis* were earlier ones *(95–97)*. It is possible that with PCR and culture techniques being refined, methodological problems prevented these groups from demonstrating evidence of the organism. Also, a large number of these studies are simply case reports, albeit with acceptable number of patients, and only one is a case–control study *(96)*. It is possible that the presence of *C. trachomatis* merely reflects changes in the local flora after prolonged use of antimicrobial agents *(66)*.

Mycoplasma

Mycoplasma species are among the smallest free-living organisms. They are unique among prokaryotes in that they lack a cell wall. This explains their negative gram strain reaction and the non-susceptibility to many antimicrobial agents. *Mycoplasma* organisms are usually associated with mucosae. They reside extracellularly in the respiratory and urogenital tracts and rarely penetrate the submucosa. Being almost impossible to grow by conventional means, our understanding of these organisms is rather limited. For this very reason, diagnosis is through molecular techniques. Our understanding of their implication in human health and disease is still in its infancy, but rapidly progressing. *Ureaplasma* also belongs to this group.

Groups that have looked for *Ureaplasma* spp. in patients with CP/CPPS have usually found it in a small but significant proportion of patients *(89,90,93, 98–103)*. But again, this finding is not universal, and at least one group reported the absence of *Ureaplasma*

spp. in patients with CP/CPPS *(97)*. It is generally agreed that *Mycoplasma hominis* is not implicated in CP/CPPS *(97,100,101)*.

Other Micro-Organisms

Isolated reports link CP/CPPS with other micro-organisms. One can make such a case for *Trichomonas vaginalis (89,104,105)*, *Burkholderia pseudomallei (106)*, and anaerobic bacteria *(97)*. None of these studies were controlled and were also subject to the usual bias of urethral contamination. Another novel observation is the possible link between putative nanobacteria and CP/CPPS, particularly in patients with concomitant prostatic stones *(107)*. Nanobacteria have attracted attention of late through their possible implication in biomineralization *(108)*.

Conclusion of Micro-Organism as Etiology

Micro-organisms are commonly found in men with CPPS. What is still unknown is how to differentiate true pathogens from commensal bacteria and how to determine cause and effect. It may also be that infection is clinically relevant only in a subset of patients. We have seen that micro-organisms can be identified in about 10% of patients suffering from CP/CPPS. Another possibility is that micro-organisms are inducers of an immunological/inflammatory cascade that ultimately leads to chronic inflammation of the prostate. If this hypothesis has merit, finding micro-organisms in the prostate would be irrelevant in a large subset of patients with CP/CPPS, as the cascade has already been initiated.

Inflammation/Immune Dysregulation

Inflammation has long been suspected to have an important role in CP/CPPS, whether in response to infection or as an autoimmune condition. There is evidence that the local immune system of the prostate is activated after chronic bacterial prostatitis, as prostatic fluid IgA and IgG are elevated while no serum immunoglobulin elevation is detected *(109)*. Following the resolution of the bacterial episode, elevated IgA levels in prostatic fluid persists for at least 2 years *(110)*. Similarly, level of IgA in prostatic fluid has also been linked with exacerbation of symptoms *(111)*. Using prostate biopsy in both healthy controls and patients suffering from CP/CPPS, another group has linked antibody deposition in the prostate with clinical symptoms *(112)*. It has also been observed in the prostatic secretions of men with CP/CPPS that antibodies directed against gram-negative bacteria are present at significantly higher level, providing an interesting bridge to link an initial bacterial infection with the cascade that ultimately ends up with CP/CPPS *(113)*.

There is also convincing evidence suggesting that the local environment of the prostate in men with CP/CPPS is altered toward an inflamed state. C-reactive protein has been found in higher level in the serum and semen of men with CP/CPPS especially those with fertility problems *(114)*. Similar findings have also been reported using other markers of inflammation *(115)*. Another group, however, could not link CP/CPPS with abnormalities in sperm analysis *(116)*. Reactive oxygen species (ROS), a marker of inflammation, and its effects are also elevated in the semen of men with CP/CPPS, but not in the semen of asymptomatic healthy controls *(117)*. The previous study could not, however, link leukospermia, ROS and symptoms, in the same way that WBCs and symptoms could not be casually linked *(47)*. In an attempt to link inflammation and

pain, it has also been demonstrated that lower beta endorphin (pain modulation) and higher prostaglandin E_2 (inflammation) were present in CP/CPPS. Successful treatment with antioxidants or antibiotics resulted in lower PGE2 and higher beta endorphin *(118)*.

Cytokines have also been found in EPS of men with CP/CPPS. Interleukin-6 (IL-6) and 8, known pro-inflammatory cytokines, are significantly elevated in prostatic secretions of men with CP/CPPS when compared to healthy controls *(119)*. Similar observation have been made for IL-1 and tumor necrosis factor (TNF) *(120,121)* and for interferon-gamma and IL-2 *(122)*. The anti-inflammatory cytokine IL-10 has also been found in higher level in patients with CP/CPPS and to correlate with various symptom scores *(122)*. We have shown that men with CPPS were more likely to have a genotype of low IL-10 production. Moreover, genetic polymorphisms for IL-10 and TNF helped predict treatment response *(123)*.

An autoimmune etiology for CP/CPPS has also been suggested. Prostate-specific antigen (PSA) has been proposed as a potential auto-antigen in a subset of men with CP/CPPS, with the demonstration of a proliferative CD4+ T-cell response to PSA *(124,125)*. Other antigens have also been proposed *(126–128)*. Although an autoimmune etiology for CP/CPPS is intriguing, it appears to apply, at best, to a small subset of patients (i.e., granulomatous prostatitis).

Dysfunctional Voiding

Urodynamic studies have been performed in patients with CP/CPPS in an attempt to further categorize patients and to provide treatment options. It has been reported by some groups that patients with CS/CPPS present urodynamic evidence of bladder outlet obstruction *(129–133)*. It has also been reported that a subset of these patients have ultrasonographic evidence of bladder neck hypertrophy *(134)* and that uroflometry in these patients presents an obstructive pattern *(135)*. It has been hypothesized that this dysfunctional voiding brings about an overstimulation of the pelvic automonic nervous system that eventually lead to chronic pain. Dysfunctional voiding may be a significant factor; however, it is probably not the predominant factor in the majority of men suffering from CP/CPPS *(130)*. Not all groups have found utility with urodynamic testing *(136)* and we use is sparingly in CPPS patients.

Intraprostatic Pressure

The prostate is an encapsulated organ and as such may become painful from increased intracapsular pressure *(137–139)*. As a corollary, it has also been reported that patients suffering from CP/CPPS have higher blood flow to the prostatic capsule and parenchyma, as assessed by color Doppler ultrasonography *(140)*. These observations are intriguing, but have yet to be validated by other groups and, ideally, should translate into treatment options.

Interstitial Cystitis-Like

Interstitial cystitis (IC) is a syndrome of bladder pain and frequency in the absence of other defined pathology. Its prevalence is difficult to assess but is believed to be around 10% in the general population *(141)*. Most estimates claim that about 10% of IC patients are male. Compared with typical CPPS symptoms, men with IC are more likely to have severe frequency and suprapubic tenderness to palpation *(142–144)*. Pentosan polysulfate (PPS, Elmiron) is an oral agent used for the treatment of interstitial

cystitis which shows modest benefit to reduce IC symptoms in some patients. An early small double-blind randomized study *(145)* in men with CPPS showed some benefit. A more recent larger double blind placebo-controlled study showed a slight benefit in symptoms with PPS; however, the results did not achieve statistical significance.

Neuromuscular Spasm/Autonomous Pain Syndrome

All pain is ultimately a "neurological" condition. Infection and inflammation can lead to nerve irritation and local muscle spasm, which will resolve when the infection and inflammation are eliminated. Pelvic muscle spasm on its own in the absence of any prostate pathology can mimic the symptoms of CPPS. Therefore, some patients with CPPS have neuromuscular spasm as their primary etiology and others may develop it secondary to repeated bouts of infection or inflammation. These issues are discussed in greater depth in other section of this book.

Multifactorial Etiology

The possible etiologies presented above all have data to support them although they may at times appear mutually exclusive. It is likely that the syndrome of CPPS has different causes, much as the "syndrome" of headache does. It is also plausible that patients have a multifactorial etiology, which is certainly supported by many patient's clinical history. There may be an initial UTI or STD which is untreated or partially treated by antibiotics, leading to an inflammatory reaction. This inflammation may persist after the infection is ultimately cleared. Persistent inflammation can lead to autonomous muscle spasm that persists after the inflammation is cleared. Muscle spasm can lead to residual urine which can lead to a new UTI. Prolonged pain and disability can produce central neurological changes that increase physical and psychological responses to painful stimuli. Therapy may therefore not be successful unless and until all the contributing factors are treated.

TREATMENT

Antimicrobials

It has been presented in previous sections that CP/CPPS may, at some point in the natural course of the disease, be caused by infection. Although uropathogenic bacteria are actually cultured from a minority of CP/CPPS patients, antimicrobial therapy is the most commonly prescribed treatment *(3)*.

Our knowledge of drug pharmacokinetics in the prostate is limited. Using the dog as a model, it was found that antimicrobials could be detected at very low concentration in the prostate despite adequately high-plasma concentration *(146)*. As infection alters permeability of drugs in various organs, animal models were created to account for infection of the prostate and its local effects *(147)*. It was thus reported that trimethoprim, but not sulfamethoxazole or penicillin, could concentrate in prostatic secretion and prostatic interstitial fluid *(147)*. Central to the understanding of drug diffusion into inflamed or normal prostate is the acid/base aspect of each drug or its pKa. In the dog model, drugs with higher pKa, or weak bases, can concentrate into the prostatic secretions.

The pH of prostatic secretion in normal men is around 7.3 and it can reach 8.3 during infection *(148–151)*. This observation suggested that the prostatic concentration reported using the animal model may not be clinically relevant. Building on these studies and with techniques of their own, a group from Germany has published some interesting observations regarding the penetration of fluoroquinolones in the prostate (reviewed in *(152)*). They thus presented the following ranking of fluoroquinolones (from low to high) according to prostatic fluid concentration: norfloxacin < ciprofloxacin < enoxacin < ofloxacin < fleroxacin < gatifloxacin < lomefloxacin. In seminal fluid, the order is different (from low to high): gatifloxacin < lomefloxacin <ofloxacin < enoxacin < ciprofloxacin < fleroxacin.

Prostatic tissues are best penetrated by drugs with high pKa and lipid solubilities (quinolones, macrolides, and sulfa drugs). Because of these pharmacokinetic properties, the quinolones are often the drug of choice in treating patients with CP/CPPS. The fluoroquinolones also have a broad spectrum: gram-negative, gram-positive (especially newer quinolones), Chlamydia, and mycoplasma. In non-placebo-controlled studies, ciprofloxacin, levaquin or lomefloxacin have proven effective in patients with CP/CPPS *(153–155)*. Two placebo-controlled study involving quinolones, namely levaquin and ciprofloxacin, found no significant effect when compared with a placebo *(156,157)*. Macrolides also penetrate well in prostatic tissue *(158)* and have been studied with some success but without placebo control *(159–161)*.

There are numerous pitfalls when one tries to assess the efficacy of antibiotics in patients with CP/CPPS. Many of the above cite studies have methodological shortcomings such as small sample size, absence of placebo control, and different outcome measures. Indeed, a critical analysis of the interventions in CP/CPPS found in the Cochrane Database of Systematic Reviews goes so far as to conclude that available data does not support any of the treatments currently used in CP/CPPS *(162)*. Furthermore, we know little of the natural course of the disease. Also, at this point, it is not possible to predict response to antibiotic treatment in patients with CP/CPPS *(163)*. The observed effect of antibiotics in some of the trials could be explained by a strong placebo effect or through some other mechanism of action not related to the bactericidal properties of the drugs *(164)*. Many antibiotics, especially quinolones and macrolides, have powerful anti-inflammatory effects independent of their ability to kill bacteria. Another unresolved issues is whether or not bacteria in prostatic tissue survive in a milieu protected by biofilms *(165)*, as it may affect antimicrobial choices.

Despite continuing controversy, antimicrobial agents are the most common therapy employed in the treatment of CP. While some patients with non-bacterial (category III) prostatitis do improve with antibiotics, prolonged courses in the absence of documented infection or symptomatic improvement are not warranted.

Anti-Inflammatory Agents

As presented above, a large body of literature supports role for inflammation at some point in the disease process of CP/CPPS. Conceptually, drugs with anti-inflammatory properties could alleviate at least some symptoms.

Canale et al. demonstrated some efficacy of ketoprofen suppository in patients with CP/CPPS *(166)*. This study, however, was neither blinded nor placebo-controlled. There is only one well-designed, placebo-controlled, randomized trial with an anti-inflammatory agent in patients with CP/CPPS *(167)* in which a marginal effect was observed. Unfortunately, the drug used, namely rofecoxib, has been voluntarily

withdrawn by its manufacturer. Corticosteroids are also potent anti-inflammatory agents. In a very small non-controlled study, it has been reported that prednisolone was effective in relieving symptoms in patients with CP/CPPS *(168)*. One must obviously weigh the risk and benefits of using corticosteroids and their multiple and significant side effects.

Alpha Blockers

Patients with CP/CPPS frequently present with LUTS of an irritative or obstructive nature, as previously discussed. Some groups have presented data suggesting that bladder neck obstruction was instrumental to the symptoms. This dysfunctional or high-pressure voiding may lead to reflux of urine within the prostate, ultimately causing inflammation and/or pain. Potentially, alpha blockers by relaxing the bladder neck could improve urinary flow, thereby decreasing intraprostatic reflux. In addition, there are alpha-1 receptors in the spinal cord which can be targets for these drugs to relieve pain independently from their direct effects on the lower urinary tract.

A well-designed study with alfuzosin in patients with CP/CPPS demonstrated modest, but statistically significant, improvement in the NIH-CPSI score *(169)*. The effect was only apparent after several months of treatment and disappeared when treatment was stopped. Tamsulosin was also the subject of well-designed studies. One study reported that tamsulosin was superior to placebo *(170)*, whereas another study reported no differences *(171)*. Discrepancies in the patient population may account for the differences. Terazosin has also been effective for CPPS when compared with placebo *(172)*. Until larger definitive trials are completed, it is reasonable to give CPPS patients a 3-month trial of an alpha blocker such as alfusozin or tamsulosin.

Hormonal Manipulations

The prostatic stroma depends on hormones for its development, and the effects of androgen deprivation on the prostate are well known. In two animal models of CP/CPPS (rats and dogs), it has been demonstrated that androgen deprivation could positively affect the course of prostatitis *(173,174)*. In men with CP/CPPS, a non-controlled study comparing saw palmetto and finasteride concluded that finasteride but not saw palmetto could offer significant and durable improvement to patients *(175,176)*. Nickel et al. found that finasteride could offer symptomatic relief to some patients. The effect was, however, small, and the authors did not recommend the use of finasteride as monotherapy, unless patients present concomitant evidence of BPH.

Prostate Massage and Ejaculation

Prostate massage was the mainstay of treatment in prostatitis prior to the availability of antibiotics *(177)* but has fallen from favor. This form of therapy may however, be regaining some of its popularity, mainly because of the failure of standard medical therapy in patients with CP/CPPS. Conceptually, repeated prostate massage may help drain occluded prostatic duct and improve antibiotic penetration in the gland *(178)*. In a non-controlled study *(179)*, prostate massage two to three times per week for 4–6 weeks together with antibiotic treatment had some benefit. Frequent ejaculation may achieve a similar effect *(180)*. In another study, 40% of patients were improved by antibiotics with prostate massage, particularly if there was a large volume of prostate

fluid on the first visit, if the patient had symptomatic relief from the first massage, or if prostate cultures remained positive despite appropriate antibiotics *(181)*.

Surgery and Minimally Invasive Therapy

Surgery does not have an important role in CP/CPPS, unless a specific surgical indication is uncovered during investigation. Radical TURP for CPPS was tried in the 1980s *(182)* but has been abandoned as few patients improved and many worsened. Minimally invasive therapies have also been advocated for CP/CPPS. Transurethral needle ablation of the prostate showed benefit in an open label study *(183,184)*. However, a sham-controlled study concluded that the efficacy of TUNA was comparable to sham treatment, and therefore TUNA cannot be recommended as treatment of CP/CPPS *(185)*. Transurethral microwave therapy (TUMT) has also been studied in patients with CP/CPPS and was shown to be effective in non-controlled studies *(186–190)*. These results are promising, but obviously a sham-controlled trial is needed.

Alternative Medicine

Several alternative or complementary therapies have been tried in men with CP/CPPS and a few even have placebo-controlled studies to support them.

Some studies have been presented with favorable data in patients with CP/CPPS treated with acupuncture *(191–193)*. However, none of these studies are adequately controlled, which would be simple to do.

Phytotherapy is another such alternative to standard medical treatment. A large number of plant extracts have been used for the treatment of CP/CPPS. Examples include Chinese herbs *(194–197)*, green tea extracts *(198)*, quecertin *(199,200)*, and bee pollen *(201–203)*. The only therapies with placebo-controlled trials are saw palmetto, quercetin, and bee pollen.

Extracts of bee pollen have been used in prostatic conditions for their presumed anti-inflammatory and antiandrogenic effects. In a small open-label study, 13 of 15 patients reported symptomatic improvement. In a larger, more recent open-label study, 90 patients received one tablet of Cernilton N three times daily for 6 months *(203)*. Patients with complicating factors (prostatic calculi, urethral stricture, or bladder neck sclerosis) had minimal response, with only one of 18 showing improvement. However, in the "uncomplicated" patients, 36% were cured of their symptoms and 42% improved. Elist assessed the efficacy and safety of a pollen extract preparation for treatment patients with CPPS. In a double-blind study, 60 patients were randomized to receive Prostat/Poltit or placebo. After 6 months of therapy, the pollen extract group had greater symptom improvement than placebo although a validated symptom score was not used *(204)*.

Quercetin is a polyphenolic bioflavonoid commonly found in red wine, green tea, and onions *(205,206)*. It has documented antioxidant and anti-inflammatory properties *(207)* and inhibits inflammatory cytokines, such as IL-8, implicated in the pathogenesis of CPPS *(208)*. In a preliminary small, open-label study, 500 mg of quercetin administered twice daily gave significant symptomatic improvement to most patients, particularly those with negative EPS cultures *(181)*. This was followed by a prospective, double-blind, placebo-controlled trial of 500 mg of quercetin administered twice daily for 4 weeks, using the NIH-CPSI as the primary endpoint *(199)*. Patients taking placebo had a mean improvement in NIH-CPSI from 20.2 to 18.8 and those taking quercetin

had a mean improvement from 21.0 to 13.1 ($p = 0.003$). Twenty percent of patients taking placebo and 67% of patients taking the bioflavonoid had an improvement of symptoms of at least 25%. A third group of patients received Prosta-Q (Farr Labs, El Segundo, CA), a commercial formulation containing quercetin with bromelain and papain, which are digestive enzymes known to increase the intestinal absorption of quercetin. In this group, 82% of the patients showed a significant improvement in symptoms. Side effects are rare although gastrointestinal side effects can occur if taken on an empty stomach.

Several mechanisms may contribute to the beneficial effects of quercetin in CPPS. CPPS is associated with elevated oxidative stress in EPS and semen, and patients who improve with quercetin have a reduction in oxidative stress metabolite F2-isoprostane in their EPS *(209)*. Furthermore, quercetin therapy reduces inflammation, which is measured by prostaglandin E_2 levels in EPS, and increases the levels of prostatic beta endorphins *(118)*.

Saw Palmetto is the most commonly used phytochemical for lower urinary tract symptoms and benign prostatic hyperplasia and some of the clinical studies with entry criteria based on symptoms likely included patients with CPPS. It is unclear whether the beneficial effects are from DHT blockade, alpha-1 receptor blockade, or some other unknown mechanism. One study compared therapy with Saw Palmetto or finasteride in CPPS patients for 1 year. Although there was some improvement seen in the finasteride group, there was no improvement in the Saw Palmetto group *(176)*.

Multimodality Treatment

Ample evidence has been presented thus far in favor of a multifactorial etiology for CP/CPPS. This same multifactorial etiology may be, in part, the reason why many monotherapies have failed to demonstrate significant improvement in properly designed studies. It is intuitively obvious that a patient with both infection and inflam-

Table 2
Treatment Combinations Commonly Used for Prostatitis Syndromes in Our Clinic

Indications	Agents Used	Comments
CPPS	Antibiotics + prostate massage	Large volume prostatic fluid or immediate relief best predictors
CPPS	Quercetin + alpha blockers	First line if cultures negative. May combine with bromelain, papain, and bee pollen
CPPS with prostatic calculi	Tetracycline + EDTA suppository	Data very preliminary but favorable in our most difficult patients
Pelvic muscle spasm	Amitriptyline ± gabapentin Pelvic physiotherapy Acupuncture	Pelvic muscle spasm and tenderness detected and infection/inflammation ruled out

mation would be best served by therapy to kill the bacteria and therapy to reduce the inflammation. This may be why many studies of monotherapy have been unsuccessful.

Two studies emphasize this point. In a study by Shoskes et al., a stepwise, systematic approach to therapy with antibiotics, anti-inflammatory, and neuromuscular agents was successful in the treatment of the majority of patients with long-standing CP/CPPS *(210)*. Similar result using another systematic, stepwise approach to these patients has been presented by Nickel et al. *(211)*. Table 2 outlines the multimodal approach we use in our clinic for CPPS.

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13 Post Vasectomy Pain Syndrome

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Summary

Although the prevalence of post vasectomy pain syndrome is unknown, it is certain that the incidence of this uncommon complication will increase because of the continued popularity of vasectomy as a highly effective and economic means of contraception. This chapter covers the evaluation of and treatment options available for the sequelae of symptoms associated with post vasectomy pain syndrome and its complications. Therapeutic options are based on expert opinion and the compassionate creativity of specialists. Evidence-based treatments are not available, in part, because the exact cause of this debilitating disorder is, as yet, unconfirmed.

Key Words: Post vasectomy pain syndrome; epididymitis; sperm granuloma; genital pain; orchalgia.

Contents

Although post vasectomy pain syndrome is relatively uncommon and the failure to respond to conservative measures is rare, elective sterilization, by means of vasectomy is a fairly common procedure. Therefore, medical practitioners are bound to encounter patients suffering from this pain condition. Approximately 500,000 vasectomies are performed annually in the US alone. It is considered to be a highly effective as well as economical means of contraception. Most vasectomies are performed in an outpatient setting and are associated with a low risk of complications.

Early complications include superficial wound infections, testicular or epididymal congestion, scrotal echymosis, and minor hematoma. Major complications such as hematomas and septic epididymitis are rare.

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Late complications include recanalization or undesired restoration of fertility, erectile dysfunction, sperm granuloma and decreased libido. The incidence of these late complications is considered to be exceedingly low. Other potential long-term sequelae, such as atherosclerosis, anti-sperm antibodies, prostate cancer, and testicular cancers, have been examined. Such correlations lack evidence and can be safely considered speculative.

Although little is known about the actual incidence of post vasectomy pain syndrome, one group of investigators (Choe et al.) believe it is the most common complication of vasectomy with the greatest potential to adversely affect the quality life of men undergoing this procedure.

The incidence of post vasectomy pain syndrome has been reported to be between 3 and 8%. However, there are reports of higher incidence, which may represent previous underreporting and currently improved recognition of this entity, or perhaps an artifact of study design, namely the assessment by means of surveyed responses. Choe and colleagues sent surveys to 470 patients. Of the 42.3% who responded to the survey, 18.7% reported chronic discomfort, although most of those described it as occasional and not troublesome. Nearly 10% of men, however, were dissatisfied with their vasectomy, 10/13, citing scrotal pain as the reason.

McMahon and colleagues conducted a postal and telephone survey of 172 patients, 4 years following vasectomy. A total of 56 men (33%) acknowledged chronic testicular discomfort, 26 of these, or 15%, considered it troublesome. Of note, however, is that only 5% of men sought medical attention for this condition.

According to McMahon's survey, about half of the patients who reported post-operative complications in general, experienced long-term discomfort. However, no correlation was found between immediate post-operative problems such as hematoma, bleeding or infection, which might otherwise imply a relationship between the operative technique or skill of the surgeon and the risk of chronic pain. It is important to bear in mind the powerful role of recall bias in this setting.

Anecdotally speaking, we have frequently observed the post vasectomy pain syndrome in men who had undergone vasectomy during a time of stress. One man, for example, had undergone vasectomy almost immediately after spouse's unplanned/undesired pregnancy. In yet another example, a man described a 6-year history of debilitating scrotal pain for which he was unable to offer a precipitating event. However, after persistent inquiry he exclaimed, "I got this vasectomy, and she left me anyway!"

Symptoms of post vasectomy pain syndrome include unilateral or bilateral testicular pain, which may be perceived as a constant dull ache or severe, debilitating pain, which may be exacerbated or precipitated by sexual arousal, intercourse and/or ejaculation. See Table 1, modified from Nangia et al.

Onset of symptoms is surprisingly variable. Surgeons studying their own small series of vasectomy reversal or epididymectomy candidates, cite the onset of pain as early as the immediate post operative period to as late as 5–7 years following the sterilization procedure. In one series, a patient's symptoms began 20 years after vasectomy. Nangia reported the onset of pain an average of 2 years after vasectomy, and in this series, intervention by means of vasectomy reversal occurred a mean of 4.8 years after vasectomy.

Some patients have described intermittently swelling of their scrotal contents correlating with exacerbation of pain. In one case report, which involved epididymectomy

Table 1
Surgical Alternatives for Chronic Pain Attributed to Vasectomy

Author/Year	*Surgery*	*Number of patients*	*Response (%)*
Schmidt, 1979 *(10)*	Exc granuloma	63	?
Chen, 1991 *(3)*	Epididymectomy	10	50
Selikowitz, 1985 *(11)*	Epididymectomy	18	94
Shapiro, 1979 *(12)*	Vasectomy reversal	6	100
Myers, 1997 *(7)*	Vasectomy reversal	32	75
Nangia, 2000 *(8)*	Vasectomy reversal	13	69

for post vasectomy pain, a painful "variable scrotal mass" was presumed to be an intermittently obstructed cystic tubule identified at the time of surgery.

On clinical exam, investigators have emphasized the absence of urinary or prostatatic abnormalities. Tenderness, however, may be elicited by palpation of the scrotum and the scrotal contents. Conversely, physical examination may reveal no objective findings to corroborate testicular tenderness, which may imply an inability for patients to accurately localize their pain symptoms. The epididymides may be palpably engorged or endurated. Both tender and nontender sperm granuloma may be detected. Ultrasonography may demonstrate epididymal cysts, but these nonspecific findings, as they are more frequently observed in vasectomized patients.

Many theories have been put forth with respect to the etiology of post vasectomy pain syndrome. Infection has been proposed as the cause of this syndrome. Other possible causes are testicular engorgement, epididymal congestion, nerve entrapment, extravasation of sperm or sperm granuloma, although the latter is considered by some to be a separate diagnosis, and not part of the post vasectomy pain syndrome (Sperm granuloma will be discussed in greater detail below).

Although infection seems like an attractive explanation for chronic testicular or epididymal pain following vasectomy, evidence for this is lacking. In their series of 18 patients, Selikowitz and Schned obtained preoperative urinary cultures as well as several cultures of epididymal tissues, which demonstrated no bacterial or fungal growth. Nangia and colleagues performed vasectomy reversal on 13 men who had no evidence of infection and had been treated unsuccessfully with one or more courses of antibiotics.

Several authors have described the resolution of symptoms by means of conservative or non-surgical intervention. Antibiotics, Non-steroidal anti-inflammatory drugs, sitz baths and scrotal support have been the recommended first-line therapies. Unfortunately, there are no studies stratifying or quantifying response rates for these treatments.

The role of subclinical

Selikowitz and Schned emphasize "late post-vasectomy syndrome is secondary to long-standing obstruction of the excurrent ductal system". They concluded that although the pathological findings seen after vasectomy could be found to some degree in the control epididymides, there existed a characterisitic constellation of findings unique to post-vasectomy syndrome, namely, sperm extravasation, tubular dilatation, sperm-packed tubules and relative LACK of acute inflammatory cells, along with sperm granuloma.

Taxy and colleagues describe "subclinical" pathological changes however, concluding that some form of inflammatory-proliferative response can be expected after vasectomy or scrotal exploration for other causes, and is usually asymptomatic. They studied specimens obtained from 41 men undergoing vasovasostomy (37 had had vasectomy 1–15 years earlier and 4 were being treated for primary infertility). All patients were asymptomatic. The pathological findings from 18 of the men exhibited an invariable background of chronic inflammatory infiltrate. Three distinct lesions were observed: Vastitis nodosa, sperm granuloma and suture granuloma.

Vastitis nodosa is defined as a proliferation of discrete appearing ductules originating from the main lumen of the vas deferen, which would extend into or through its wall. In an earlier publication (1979), Schmidt uses this term to describe asymptomatic sperm granulomas, suspected to be a consequence of minor, non-progressive leakage. These are void of inflammatory changes, lined primarily with epithelial cells. This histological finding has also been described in association with inflammation and scarring at the original point of vasal obstruction during vasectomy.

Sperm granuloma is defined as an inflammatory nodule consisting of lymphocytes and histiocytes, associated with collections of spermatozoa. Sperm granuloma and vastitis nodosa have been identified together in the same pathological specimens and in men who are asymptomatic, thereby refuting the previously described differentiation between symptomatic and asymptomatic granulomas. This controversy may explain why there is such a large variation in the reported prevalence of sperm granuloma. Schmidt reported a 32% incidence of granulomas in men who underwent "ligature vasectomy", with as many as "10% having symptoms". In his own series, spanning 22 years, he diagnosed sperm granuloma in 154 men. Over one-half of the men were symptomatic, and of these, 76% required surgical excision of the granuloma to address their pain. In the smaller series of Nangia, 3 of 13 men had histologically confirmed granuloma, although only two of the men had tenderness referable to this site, preoperatively.

The pathological study conducted by Taxy and colleagues revealed a 41% incidence of sperm granuloma among asymptomatic men. Adding further to confusion over the clinical significance of sperm granuloma are the observations made by Shapiro and Silber, who conducted a prospective study in which sperm granuloma were intentionally allowed to form by performing vasectomies employing an open-ended technique. In their series, over 400 men underwent the procedure, in which the testicular end of the vas was not ligated or clipped, permitting the leakage of sperm and the [almost] inevitable formation of a granuloma. Using this technique resulted in a higher than acceptable recanalization rate of about 4% and sperm granuloma formation in 97% of the patients. None of these patients experienced pain or discomfort referable to the sperm granuloma confirmed at the post-operative visit. These patients were compared with nine men who were referred to them for post vasectomy orchialgia. Of note, two of the nine men were found to have sperm granuloma as the source of their pain. Surgical excision of the lesions resulted in complete pain resolution. The remaining seven patients were described in detail, as the authors defended the otherwise preventive or protective nature of sperm granuloma. Onset of pain following the vasectomy in these nine patients, was not documented in this study. Unfortunately, despite the compelling number of patients in this thoughtful prospective study, it is difficult to adopt this technique as a means of preventing post-vasectomy pain syndrome because follow up was no greater than 1 month and the sterilization failure rate unacceptably high.

As described in the previously cited series, investigators noted onset of symptoms for post vasectomy pain syndrome a mean 2 years after vasectomy, but also with such variability as 1 month or 20 years. Additionally, Myers and colleagues have observed the formation of painful sperm granulomas at the upper end of the testes, occurring after epididymectomy for post vasectomy pain syndrome. Some of these patients eventually required orchiectomy for the management of their pain.

Suture granulomas are defined as inflammatory reactions appreciated histologically, associated with suture or ligature. Taxy's group observed these in 51% of asymptomatic patients. In nearly half of the cases, this occurred without sperm granuloma.

Nangia and colleagues conducted a careful evaluation of signs, symptoms and histological findings in men undergoing vasovasostomy. The objective of their study was to determine whether nerve proliferation, inflammation or vastitis nodosa, identified histologically, could be correlated to patient symptoms, thereby elucidating potential causes of the post vasectomy pain syndrome. Thirteen patients undergoing vasovasostomy solely to relieve pain were carefully screened and compared with 16 controls, who were men seeking vasectomy reversal to restore fertility. Preoperatively, nearly the same proportion of men exhibited nodules at the vasectomy site and/or fullness of the epididymides. Patients were similar except for the presence of pain. Following vasectomy reversal, histological evaluation of the excised vas revealed no differences between symptomatic patients and controls. Similarity between the groups was also appreciated when specimens were matched according to time interval between vasectomy and reversal. One of the patients in whom pain resolved following vasectomy reversal, experienced a recurrence of his symptoms 1 year later. Because semen analysis demonstrated azospermia, recurrence was attributed to bilateral reocclusion of the vas deferens.

EVALUATION

Although vasectomy is a simple outpatient surgical procedure, one cannot discount the emotional complexity surrounding a patient's or a couple's choice to pursue sterilization. It is therefore essential that the patient history include query into the motivation and social milieu at the time leading up to and shortly after their vasectomy. Review of systems should be conducted with an emphasis on physical activity and exercise thresholds or limitations, urinary and bowel habits, sexual performance and satisfaction as well as social supports and emotional sanctuary. Sometimes it is helpful to observe the interaction between the patient and his or her partner or to obtain further insights from the partner during the visit.

Many patients exhibit limited range of motion and guarded movements, as they attempt to protect the genital area from the slightest manipulation. Initiating the physical exam, gently, at the head, neck and chest, helps to assuage tension and guarding, which could otherwise limit the genito-urinary evaluation. The inguinal region and genitals should be assessed both in standing and in supine positions in order to exclude hernias or varicoceles. Palpation of the groin, cord structures, testicles and epididymides should be performed methodically while the patient is in supine or lithotomy position. Ideally, the exam room and the hands of the examiner are warm. By positioning the patient in the lithotomy position, the examiner can also easily assess the adductor muscles and their tendonous insertion, as well as the perineum, anus, prostate and internal pelvic floor.

Neurological examination should be performed to exclude radicular pain syndromes, neuro-sensory deficits and symmetry of strength, tone and reflexes.

Urinalysis should be done routinely to exclude infection as well as other urinary tract abnormalities, which could manifest as referred testicular pain, such as a ureteral calculus.

Although ultrasonography does not usually provide any additional information that would confirm diagnosis or refine treatment plan, it should be considered in order to rule out the rare possibility of concomitant testicular neoplasm. It should be performed especially when the patient's pain prohibits an adequate physical examination.

Although the patient's perception is that of testicular pain resulting from a surgical sterilization procedure, the examiner must maintain a broader perspective, recognizing characteristics of referred pain and the centralization phenomena of chronic pain.

During physical examination, I have found it useful to assess posture, back and abdominal wall muscles, as well as pelvic floor myofascial trigger points. I have found active trigger points in surrounding muscles of the lower abdomen and pelvic floor in men with chronic scrotal or testicular pain, and believe that these can be generous contributors to ongoing pain syndromes. According to Simon and Travell, Myofascial Trigger Points are caused by macrotrauma, such as surgery or injury, or by microtrauma, in the form of daily disuse or misuse of muscles. As a result of macro- or microtrauma, muscles become weak, taut and shortened, which contribute to the formation of trigger points. Fatigue and emotional stress have been shown to exacerbate trigger point phenomena as well. All these factors are potent perpetuators of pain syndromes and can be identified easily in many of our patients. Myofascial pain syndromes are addressed in a separate chapter pertaining to physical therapy for pelvic pain, of this book.

TREATMENT

Men seeking treatment for post-vasectomy pain syndrome, like most patients suffering from chronic pain, are frustrated and feel misunderstood. Many patients describe a sense of alienation from healthcare providers, who are perceived to be unsympathetic to their pain and disappointment. It is, therefore, essential to exhibit genuine concern and empathy towards our patients, which is best demonstrated by the thoroughness of our interview and physical exam. I believe that no matter the prescribed treatment, all patients should be afforded appropriate attention and compassion. This is especially true because these men exhibit a sense of betrayal and a mistrust of the medical community. They associate their ongoing discomfort with a previously described low-risk, elective procedure.

Regaining trust is a valuable part of their therapy.

There are no published data pertaining to non-surgical treatments of post vasectomy pain syndrome. As mentioned earlier, not even the actual prevalence of this condition is known. The author will share her 13-year experience as a male genital pain expert at a tertiary care center, as well as review the few published surgical series.

Pharmacological Treatments

It would not be inappropriate to empirically treat a man for infection at his initial visit; however, repeated courses of antibiotics in the absence of any sign or symptom of infection, other than pain, would be useless and perhaps even harmful. Non-steroidal

anti-inflammatory drugs (NSAID), prescribed as scheduled daily dosages over a period of 2–4 weeks should be considered, because many patients have only used such medications inconsistently and/or just as needed. I have also prescribed NSAID, 1 h before intercourse for those patients whose symptoms occur during or after ejaculation. Low-dose benzodiazepines, before intercourse may benefit others in whom skeletal muscle tension and contraction are contributing factors. This form of treatment is occasionally prescribed to men experiencing dysorgasmia or painful orgasm because of other causes. It is believed that relaxation of the skeletal muscles, particularly those of the lower abdomen and pelvis, will assuage the discomfort associated with painful ejaculation.

Although tricyclic antidepressants have not been studied in this setting, they have been employed for many years for the treatment of chronic pain syndromes. Applying expert consensus and experience, this group of medications offers a safe and potentially effective alternative for pain management. I prefer to use elavil (amitriptyline) beginning at 25 mg, 2–3 h before bedtime, titrating, if necessary, every 2 weeks up to 100 mg. Newer agents such as gabapentin and pregabilin are being studied for the use of male pelvic and genital pain syndromes and may benefit post vasectomy pain patients as well.

Physical Therapy and Myofascial Trigger Point Release

This therapy is a valuable form of self-care and empowerment, but it should be prescribed when history and physical findings confirm pain distributions attributable to muscle dysfunction or myofascial trigger points. Please refer to the chapter dedicated to this subject.

Spermatic Cord Blocks

The external spermatic sheath injection for vasal nerve block, as described by Li and colleagues for vasectomies, can be employed for both diagnostic and therapeutic purposes in the setting of post vasectomy pain. Response to the local nerve block confirms potential source of the pain, which can be diagnostic. Temporary pain relief affords therapeutic benefits as pain levels may decrease over a series of weekly injections.

The vas deferens must be carefully manually localized, under the scrotal skin, separated from the internal spermatic vessels, preferably using the three-finger method developed in China. Subcutaneous injection at the injection site, with wheal formation is recommended for vasectomy, but unnecessary for this purpose. Shorter acting lidocaine, 1–2% can be infiltrated for the initial injection through a 25- to 27-gauge needle, introduced beneath the scrotal skin surface, along the vas deferens secured by the three-finger method. Aspiration should precede the injection to confirm that the needle is not located within a blood vessel. I inject up to 5 cc of 2% lidocaine on one or each side, depending upon patient's symptoms. Bupivacaine, which has a longer half-life, may be used for subsequent injections, and the anesthetic can be combined with steroidal compound such as, for enhanced anti-inflammatory benefits.

If there is no initial diminution of discomfort with well-placed injection, I do not recommend repeating this treatment. If a favorable response is elicited, if even short-lived, I schedule weekly injections for upto 3 weeks.

Acupuncture

Acupuncture is considered the earliest form of neuromodulation. Although it remains classified as an alternative form of therapy, we are employing this modality more frequently and at earlier stages for our patients with chronic genitourinary pain.

Because there are many similarities between patients suffering from CP/CPPS associated with testicular pain and post vasectomy pain syndrome, I cite a study in which acupuncture was tested as a treatment for men diagnosed with CP/CPPS.

Authors Chen and Nickel, conclude that the favorable response to acupuncture supports the hypothesis of a neuropathic pain syndrome as the cause of patient symptomology.

Surgical Interventions for Post Vasectomy Pain Syndrome

For some patients, medical and supportive therapies are not helpful. Pain and disability may be so severe patients themselves seek more aggressive solutions. The percentage of men who undergo surgical intervention to relieve post vasectomy pain is unknown. Conclusions about response rates to surgery must be made with caution, as they are based only upon a few published series.

As one can see, these series include very small numbers of patients. Duration of symptoms before treatment was widely variable and follow up, for the most part, was relatively short. Although Schmidt advocated surgical excision of painful sperm granulomas, his publication does not document the actual percentage of successful treatments. Chen's series includes 15 procedures in 10 patients, as some men suffered from bilateral pain. Twelve specimens were submitted for histological evaluation that revealed interstitial and perineural fibrosis, which may have contributed to the painful symptoms of the post vastectomy pain syndrome. The series by Selikowitz, boasts a 94% response rate, with resolution of post vasectomy pain in 17 of 18 patients, usually within 24 h of epididymectomy. Specimens obtained from these patients demonstrated features of chronic obstruction, believed to be the source of pain. Risk of epididymectomy, however, includes the formation of sperm granuloma arising from the testicle, which may cause pain and require additional ntervention, even orchiectomy.

Vasectomy reversal is an attractive solution as it may restore the natural presurgical state of sperm flow, reversing the congestion or obstruction suspected to cause chronic discomfort. Certainly, this likewise translates to restoration of undesired fertility. Nangia and colleagues observed no histological differences between the two groups of men undergoing vasectomy reversal; however, more than half of those diagnosed with post vasectomy pain syndrome were cured by microsurgical repair to restore sperm flow.

CONCLUSIONS

Although the prevalence of post vasectomy pain syndrome is unknown, it is certain that it will increase because of the continued popularity of vasectomy as a contraceptive alternative. Therapeutic options are based on expert opinion and the compassionate creativity of specialists. Evidence-based treatments are not available, in part, because we have yet to confirm the cause of this sometimes debilitating disorder.

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14 Converging Perspectives in the Treatment of Chronic Prostatitis/Chronic Pelvic Pain Syndrome Symptoms

Dean A. Tripp, PhD

SUMMARY

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a common urological condition characterized by persistent pain in the perineum, pelvic area, and/or genitalia but exhibiting noted symptom variation in men across socioeconomic status, race, and age. Treatment using a biopsychosocial model must focus on providing the individual with specific techniques designed to help increase feelings of control over-persistent and problematic symptoms. The research reviewed emphasized wide variability in patients' responses to pain and biomedical treatment as a likely outcome predicated by the individual's prior history with pain, their cognitive appraisals and behavioral coping responses, the social milieu in which the pain occurs, and the course of the pain pathophysiology. CP/CPPS should not be viewed from a restrictive biomedical model because pain is not a purely physical phenomenon, but rather a complex physical, emotional, and interpersonal fusion, where the negative outcomes are suggested to advance over time if left unchecked.

KEY WORDS: Chronic prostatitis; chronic pelvic pain; CP/CPP; gate control theory; cognitive-behavioral therapy.

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Prostatitis has been a frustration for general practicing physicians, urologists, and patients for most of the last century. Prostatitis has been difficult to diagnose and categorize *(1)* with point prevalence estimates indicating that it is one of the most common urological conditions with noted symptom variation in men across socioeconomic status, race, and age *(2)*. Prostatitis is the most common urologic diagnosis for men under 50 years and in men over 50 the third most common *(3)*. Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) has particularly high prevalence estimates worldwide (i.e., 16% North America, 14% Asian & Europeans; *(4,5)*) and is eight times more common than chronic bacterial prostatitis *(6)*.

Persistent pain in the perineum, pelvic area, and/or genitalia are the characteristic symptoms of CP/CPPS *(2,7)*. As found in many pain conditions, CP/CPPS pain does not seem to strongly correspond with biomedical findings and no standard pathology has been documented to date *(8,9)*. CP/CPPS pain and the suffering it brings to the patient is significant and has been contrasted with benign prostatic hyperplasia *(7,10,11)*. CP/CPPS pain (i.e., perineal, abdominal, testicular, penile, and ejaculatory pain) is longstanding with little prospective change noted. For example, samples have reported CP/CPPS symptoms without effective or lasting relief for an average of 87 months *(12)*. In a broader sense, pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage *(13)*; a definition mandating that the psychology of the patient be examined for patient impact. Pain is the cardinal CP/CPPS symptom and is now being discussed, evaluated, and researched by experts outside of Urology. In a recent NIH-sponsored meeting on chronic pelvic pain, it is noteworthy that over 50% of the discussion centered on the psychosocial aspects and potential management models for CP/CPPS *(14)*.

CP/CPPS symptoms have significant negative impact on patient Quality of Life (QOL) and is comparable to other debilitating medical conditions such as active Crohn's disease, congestive heart failure, and severe diabetes *(15,16)*. Experts suggest the etiology of CP/CPPS is poorly understood *(17,18)*, that the biomedical treatment options are suboptimal *(19)*, and CP/CPPS pain chronicity is extremely difficult to manage in urological practice *(20,21)*. The etiology and pathogenesis of prostatitis-like symptoms have yet to be determined despite the numerous efforts of basic scientists and clinical researchers *(18,22)*. Although pain complaints are the most prominent and disabling clinical manifestation of CP/CPPS for many, strong psychological manifestations such as depression have also been reliably reported *(23–25)*. When considered together, the expert opinions, the biomedical data, and the chronicity of symptoms such as pain, calls into question the ongoing uni-biomedical management of CP/CPPS.

This chapter seeks to provide information and concepts that examine CP/CPPS as a chronic pain condition from a biopsychosocial perspective. It is suggested that such an interpretation of this syndrome is useful in promoting greater understanding of how the psychological and environmental deficits reported in men suffering from CP/CPPS are associated with high pain, disability, and ultimately a lower QOL. In particular, this chapter will present the basic tenets and contrasts of the biomedical and biopsychosocial model (BPSM) of pain, the status of efficacious treatment for CP/CPPS, followed by a review of recent CP/CPPS data that has direct implications

in regard to psychological and environmental contributors to pain, disability, and overall QOL. Finally, an empirically based therapeutic cognitive-behavioural model of symptom management is described.

THE BIOMEDICAL MODEL

Egan and Krieger *(9)* stated that male pelvic pain was of no interest to pain researchers, noting that less than 1% (0.08%; 2 publications) of the research over a 10-year period identified perineal or genital pain in their titles, and that only one case report mentioned male genital pain (0.04%; *(26)*). Furthermore, they suggested that CP/CPPS be considered as a chronic pain condition. The consequence of recognizing CP/CPPS as such would allow a large group of symptomatic men the hope of a different treatment perspective, including the strong investigation of pain complaints and their psychological effect. Such a classification would also prompt treatment changes, through collaborations between chronic pain specialists and urologists. Echoing the sentiments of McNaughton-Collins *(27)*, CP/CPPS symptoms are associated with poorer QOL and understanding the predictors of the prominent CP/CPPS symptoms is essential to furthering patient care.

It is no mystery as to why urologists report frustration in treating CP/CPPS. Chronic pain can stress the health care provider as well as the patient, especially as the patients report of continuing exasperation following non-curative treatments for pain. Chronic pain is associated with strong demoralization of the patient because they face the ongoing stress of pain and the ongoing difficulties that pain creates in other areas of their life (e.g., loss of work, limits on previous social activities, strained familial relations). Most patients in chronic pain seek out medical relief but report these pursuits to be evasive and wearisome. Indeed, many of these people report helplessness, hopelessness, and depression, but not all do. It may come as a surprise to some to learn that greater pain or notable radiographic deterioration is not completely associated (i.e., 1:1 ratio), with reported disability, with pain and disability being associated only modestly (e.g., *(28–30)*). It is this intrinsic spread in variance or increased unpredictability in patients suffering from chronic pain-related symptoms that we examine next.

Current pain concepts of pain and individual differences in pain perception are shaped by centuries of theoretical writings and major shifts in both culture and science *(31)*. The roots of the biomedical model can be traced back to Grecian medicine or earlier but many scholars point to the writings of Rene Descartes (1596–1650) and his argument for a dualistic approach to pain as a cornerstone to the biomedical model of pain *(31)*. From such foundations, the biomedical model of pain assumed that reported pain was equivalent in the amount of observable physical pathology *(32)*. Most importantly, Descartes argued that mental aspects of the person (i.e., mind) were separate entities in comparison with the body and that the mind was incapable of affecting physical matter in any manner. For Descartes, pain was a mechanical event experienced through a "straight-through" system where skin channels sent signals of alarm directly to the brain, allowing peripheral parts of the body to remove themselves from possible damage. As noted earlier, he proposed that such responses were directly related to the total or amount of damage being inflicted onto the site of the injury and ensuing pain *(31)*.

Although the dualistic approach to pain was common in medicine well into the nineteenth century, pain research in the 1950s provided impetus to a growing dissatisfaction with a constricted sensory model of pain. Individuals high in anxiety also

commonly reported significantly greater pain, which was significant in demonstrating the importance of psychological status in determining pain experience (e.g., *(33)*). Other pain research disagreed with the pure biomedical model in dramatic style. For example, Beecher *(34)* assessed requests for pain medications from soldiers taken to hospital for follow-up treatment of war wounds incurred at the Battle of Anzio. Comparing soldiers' requests for pain medications with those of civilians who had undergone similar clinical procedures, he noted that only 25% of the wounded soldiers requested pain medications, with other soldiers denying the existence of pain or suggesting they were experiencing very little pain and no need for pain medications. In the civilian group undergoing similar medical procedures, 8 of 10 patients requested pain medication. Beecher suggested these individual differences were the result of psychological factors, which could significantly affect pain experience or at least it's the expression. He suggested that soldiers with injuries significant enough to create a discharge from active service may have experienced strong positive emotion that acted to counter their pain experience and thus need for medication.

With the seminal works of Melzack and colleagues *(35–37)*, pain experience was promoted as a complex perceptual and individualistic experience. The "Gate Control Theory" of pain, attempted to explain both the clinical experience of pain and to address the shortcomings of previous pain models in regard to cognitive influences on pain experience and expression. The Gate Control Theory asserted there are physiological pain pathways in which their activity can either augment or reduce the subjective experience of pain. There were two major systems proposed: afferent pathways in the nervous system, where pain signals travel to the brain from the extremities, and efferent pathways, where the neurophysiological influence of emotions and cognitive activity travel down the spinal cord and modulate incoming afferent signals at the dorsal horn. Thus, strong negative emotional states act to increase subjective reports of pain by facilitating sensory processing, whereas positive emotional states may act to decrease subjective reports of pain by decreasing afferent processing *(38)*. This basic gating of pain was not described as all-or-nothing, but was suggested to be associated with the severity or amount of distress experienced by the individual. Therefore, individuals anxious about undergoing a medical procedure or who are nervous about pain in general are more likely to experience and report greater pain. The theory further stipulated that pain is not entirely a sensory experience but can be considered an experience subject to great variation from person to person, influenced by an individual's subjective meaning of the situation, attention, and other appraisals made by the individual *(36)*.

The Gate Control Theory has been significant in understanding pain experience and fostering research and has provided significant theoretical support for a multitude of pain treatments. For example, advances in pain treatment that are theoretically rooted in the Gate Control Theory include nerve stimulation through transcutaneous devices *(39)*, heat, ice *(40)*, as well as various psychological therapies such as relaxation *(38)*. Subsequent pain models focus on psychological cognitive appraisals of pain, with environmental influences, physical factors, or pain control perceptions also considered. Turk and colleagues described a cognitive-bio-behavioural perspective of pain in hopes of addressing the importance of environmental factors as well as the individual cognitive factors on pain perception *(41)*. In this model, the emphasis is placed on how an individual interprets or appraises their pain experience in light of physical sensations, emotional state, and environmental support. For example, if an individual believes he or she have poor coping skills (i.e., an inability to self-manage a particular

situation or physical sensations), or that the environment is not supportive in some manner to assisting them in managing their pain (e.g., medical staff or supportive other present or immediately available), such factors may combine and manifest different degrees of anxiety. In turn, increases in anxiousness may be related to helplessness and such negative feelings are likely to exacerbate the experience of pain. As suggested in the Gate Control Theory, physiological efferent pathways may be activated by strong negative emotional states, increasing sensory processing of pain sensations that can then in turn increase a person's distress. Pain research showing the significant impact of psychosocial variables such as pain appraisals are prominent in both experimental and clinical pain samples *(29,42,43)*.

In a revision of the Gate Control Theory, Melzack *(44)* integrated his previous model with Selye's model of stress *(45)*. Termed the Neuromatrix theory, individuals are suggested to have a somewhat genetic/characteristic pattern of nerve impulses that are activated by either sensory input or central input that is independent of peripheral activation. When injured, an individual's bodily homeostasis is altered and such deviation is considered stressful for the organism, initiating neural, hormonal, and behavioural activation to restore the baseline *(45)*. Whether physiological or psychological in nature, stress also activates the limbic system, the primary area of emotional and cognitive processing. In situations of chronic activation, there is likely a predisposition for central nervous system to become sensitized to repeated patterns of stimulation, which may act as an underlying cycle in the development of some chronic pain states (e.g., fibromyalgia; *(46)*). The Neuromatrix theory is a diathesis-stress model wherein the physiological predispositions of the person interact with the acute stressors of a particular person's experiences *(47)*. In such situations, pain itself should be qualified as a stressor that can have great reduction on bodily homeostasis. Furthermore, the presence of persistent pain can keep the body in a constant state of physiological activation. Under such a physiological load, helplessness, depression, fear, or anxiety can then act to reduce the body's homeostasis further, acting to augment one's pain experience.

There are several underlying neuroanatomical pathways, neurophysiological mechanisms, and several well-known psychosocial factors involved in pain experience *(29,48,49)*. A Biopsychosocial (BPSM) of pain asserts that biological aspects of chronic illness (e.g., changes in muscles, joints, or nerves generating nociceptive input) affect psychological factors (e.g., catastrophizing, fear, helplessness) and the social context of the individual (e.g., social activity, activity of daily living, interpersonal relationships) *(50)*. Following nociceptive inputs, the perception or interpretation of this pain occurs, making individual patient characteristics central components of their adaptive and/or maladaptive responses. Individual patient responses to pain are prejudiced by long-held beliefs about one's ability or inability to manage pain. Developing over a lifetime of somatic and interpersonal experiences, low self-efficacy for pain management is rooted in a patient's belief that their pain-coping ability is not likely to help them manage their pain *(51–53)*. Beliefs of poor ability in self-management are associated with negative pain appraisals, which in turn influence subsequent coping attempts *(29)*.

The biomedical model of pain, focusing on etiological and pathophysiological explanations for persistent pain, is considered incomplete when pain is chronic. Indeed, 30–50% of people seeking primary care intervention do not exhibit a diagnosable disorder *(54)*, and up to as many as 80% of people with low back pain do not have identifiable physical pathology but significant symptoms and impairment *(55)*. In a

similar manner, recent claims are levied against urological conditions of chronic pelvic pain. As suggested by Nickel et al. *(56)*, it is acknowledged by urological practitioners that the treatment successes with patients diagnosed with CP/CPPS have been bleak, especially with data showing that treatment strategies based on sequential application of monotherapies for patients with a long history of severe CP/CPPS may be suboptimal. Other reviews of the available literature also indicate that there were few data from properly designed and implemented clinical trials on which to justify an evidence-based approach to the treatment of CP/CPPS *(57)*. Recent opinions suggest that the effective treatment for CP/CPPS remains elusive likely because of its multifactorial pathogenesis *(18)*. In summary, the biomedical model to date has not been successful in advancing an effective cure for CP/CPPS.

Persistent pain should not be viewed as just a physical or psychological phenomenon. The data suggest that the experience and perception of pain is complex and maintained by biomedical, psychosocial, and behavioral variables whose associations are likely to evolve overtime within any one person. A BPSM, viewing illness as a dynamic and reciprocal process, offers an integrated alternative incorporating physiological, psychological, and social–contextual variables that may effect and/or perpetuate pain. This model provides advantages over the biomedical model, especially when examining patient reactivity to pain by considering patient physical function, demographic, cognitive/behavioral, and environmental domains. Despite evidence supporting the importance of psychosocial variables in a variety of chronic pain conditions *(29,32,50,58–61)*, such variables remain largely unexamined with respect to CP/CPPS pain and associated symptomatology. As suggested by Potts *(62)*, for decades chronic infection of the prostate gland has been implicated as the cause of pelvic pain in many men, and despite only 5% of men showing positive prostate gland cultures many physicians and urologists have continued to prescribe antibiotics *(63)*. Potts *(62)* also suggested that causes for prostatitis-like symptoms should be expanded outside of the prostate and must include associated syndromes such as musculoskeletal pain, myofascial pain or other functional somatic syndromes.

PSYCHOLOGICAL COMORBIDITY IN CP/CPPS

Treatment using a BPSM must focus on providing the individual with specific techniques that are designed to help them increase feelings of control over persistent and problematic symptoms. For example, the BPSM for pain requires the identification of the most relevant physical, psychological, and environmental variables for the population at risk. In assisting the development of greater symptom self-management, targeted modification of sensory, cognitive, behavioural, and environmental variables are usually suggested. The CP/CPPS literature has outlined several psychological and environmental variables that are associated with poor patient adjustment (i.e., pain, urinary symptoms, QOL).

Depressive and Anxiety Symptoms

Keltikangas-Jarvinen et al. *(64,65)* showed that high rates of depression and anxiety in their CP/CPPS samples did not decrease considerably overtime. De la Rosette et al. *(66)* showed that prostatitis is associated with depression and the tendency to somatize. Anxiety, depression, and stress are comorbid with CP/CPPS symptoms *(24)*, and for some patients, stress levels have been reported as so high that the term “stress

prostatitis" was suggested. In some samples, 20% of the patients met criteria for major depression and not one of the patients reported being previously diagnosed or treated for depression *(24)*. In a prostatitis Internet survey, 78% of patients reported depressive symptoms and 5% reported thoughts of suicide *(10)*. Furthermore, when comparing CP/CPPS patients with controls, patients reported hypochondriasis, depression, and impaired sexual function *(25)*. As well as depression and voiding symptoms, issues of psychological distress and fear of symptoms have also been associated with a diagnosis of CP/CPPS *(67)*. More recently, Ku et al. *(68)* reported that depression in CP/CPPS was associated with pain and urinary symptoms but that anxiety did not share these relations. Potts et al. *(69)* suggested that CP/CPPS patients may also report functional somatic syndromes such as irritable bowel syndrome, chronic headache, fibromyalgia, and nonspecific rheumatologic and dermatologic symptoms. They also noted that depression, anxiety, sleep disorders, and alcoholism were present in their sample as was sexual dysfunction.

In combination, the reviewed data suggest that depression and other psychological issues are comorbid in CP/CPPS. The CP/CPPS depression indication is remarkable because the prevalence of depression in the general population have hovered around 5–6% *(70)*. Interestingly, clinic-based chronic pain sufferer's prevalence for depression range from 16–45% to 10–100% *(71,72)*. Depression in patients suffering from CP/CPPS may be a reactive phenomenon of loss and despair but may also be understood from a stress-diathesis model. In a diathesis model, depressive symptoms are generated by preexisting behavioral coping strategies such as avoidance, denial, or catastrophic thinking about somatic symptoms. Such predispositions can act to increase vulnerability to depression under times of extended stress, as shown in several chronic medical conditions *(71,72)*. In contrast, there are also data indicating that individuals who present with little or no predisposing depressive features are also at risk following the development of chronic pain *(71,72)*. Thus, it is best to consider emotional experiences of patients suffering pain-related symptoms on an individual basis, focusing on their particular beliefs and behaviours.

Relationship Impact of CP/CPPS

Considering the sexual nature of the symptoms manifest in CP/CPPS, it is not surprising that pain is said to interfere with interpersonal relationships. Sexuality is negatively affected by symptoms such as pain and depression. CP/CPPS depression is likely associated with a lack of healthy relationships, as depression is often accompanied by isolation *(24)*. Depression is probably not the only factor that explains why CP/CPPS is associated with difficulties in relationships. The type and significance of pain may have significant impact on patients' relationships. Patients with CP/CPPS have reported being anxious about their relationships *(73)*. More recent data highlight sexuality as an issue in the relationships of men with CP/CPPS. For example, reductions in frequency of sexual contacts are reported in 85% and more than 50% report impotence in response to symptoms such as pain *(74)*.

Pain research shows that partners of men with sexual dysfunction and partners of men with chronic pain are impacted both sexually and psychologically *(75–78)*. Until recently, no studies had examined the CP/CPPS patient couple sexual dysfunction. Smith, Pukall, Tripp, and Nickel *(79)* examined men with CP/CPPS and their partners with healthy controls for sexuality and adjustment, and patient couples reported lower sexual functioning in some domains, but were comparable to controls on

satisfaction and relationship functioning. Men with CP/CPPS reported greater sexual dysfunction and greater depression compared with controls males. Unexpectedly, men with CP/CPPS in this sample did not report significantly decreased sexual satisfaction or relationship functioning when compared with male controls. The spouses of men with CP/CPPS reported significantly more sexual pain upon intercourse and depressive symptoms compared to female controls. In addition, patients with CP/CPPS and their partners did not differ significantly from each other with regard to sexual functioning and satisfaction, relationship functioning, or depressive symptoms. These results suggest that men with CP/CPPS and their spouses may experience some sexual difficulties, but that CP/CPPS may not have a large negative impact on patients' intimate relationships. The authors suggested that the age of the patient sample and long duration of their relationship may not generalize these data to the population of men with CP/CPPS and although CP/CPPS includes many pain sites, it may be that men predominantly experience one type of pain (e.g., ejaculatory pain) are impacted differently compared to when pain is experienced elsewhere.

In summary, relationships are impacted by CP/CPPS symptoms and it may be that the treatment of depressive symptoms could prove beneficial in pain reduction (e.g., *(71)*). It is also suggested that the management of either depressive or sexual symptoms often results in improvements in the other (e.g., *(80)*). If nothing else, the data reviewed here indicate that clinicians of men suffering from CP/CPPS should note the potential associations between patient sexual problems, relationship durations, and depressive symptoms.

CP/CPPS Quality of Life

Lower Quality of Life (QoL) is associated with a variety of comorbidities in CP/CPPS *(81)*. CP/CPPS symptoms are suggested to have a similar negative effect on QoL as Crohn's disease or a recent myocardial infarct *(82)*, and studies indicate that most men with CP/CPPS report significant impairment in QoL *(83,84)*. In the Wenninger et al. study *(82)*, the most severe impact of CP/CPPS seemed to be on social interaction and CP/CPPS pain differentiates patients from BPH *(85)*. CP/CPPS pain is associated with poor QoL and overall symptoms *(20,83,86)*. Examining primary-care settings worse QoL pain was more robustly associated than urinary symptoms *(84)*. Other CP/CPPS QoL data show that pain intensity acts as the strongest predictor of QoL, even controlling age, urinary scores, depression, and partner status *(87)*. Pain severity has been identified as the most influential factor for QoL in other pain syndromes *(88)*.

Findings showing that pain is a key factor in CP/CPPS QoL may have important implications for its clinical management. Although pain is repeatedly discussed as a primary symptom of CP/CPPS and CP/CPPS is regarded as a chronic pain condition *(84)*, no previous research has focused on how pain might affect QoL, and what physical and psychological factors might best delineate the experience of pain. As suggested by Ku, Kim, and Paick *(89)*, the urological literature suggests that an in-depth biopsychosocial analysis of QoL determinants and other important symptoms associated with poor CP/CPPS QoL (i.e., pain) is warranted. There are many psychological factors involved with appreciating QoL and pain, including social support, pain-coping strategies, cognitive appraisals of pain.

THE BIOPSYCHOSOCIAL CP/CPPS DATA

CP/CPPS outcomes of pain and disability have recently been examined using a BPSM with physical, cognitive-behavioral, and environmental predictors *(43)*. North American men enrolled in the NIH-funded Chronic Prostatitis Cohort Study completed surveys examining pain, disability, urinary symptoms, depression, catastrophizing, patients' perceived control over their pain, pain contingent rest, social support, and solicitous responses from a significant other. Greater urinary symptoms, depression, and increased catastrophizing (i.e., a pervasive negative cognitive orientation to pain that may involve excessive rumination about pain, a magnification of the threat value of pain sensations, and feelings of low ability to manage pain: feeling helpless) predicted higher pain report. Furthermore, when pain reports were broken down into their affective and sensory pain components, higher affective pain (i.e., pain described in terms of emotional descriptors such as sickening or fearful) was associated with greater depression, but elevations in catastrophizing (i.e., helplessness subscale) were the strongest pain predictor. The helplessness reported by these men is an important clinical feature of affective pain because its impact remains significant when other variables such as demographics, urinary status, and other environmental predictors are included in the analyses. A similar analysis for sensory pain (i.e., pain described in terms of physical sensations such as throbbing, sharp, aching), helplessness catastrophizing was again shown to be a strong predictor of pain along with elevations in urinary symptoms. In regard to CP/CPPS disability, worse urinary symptoms and pain predicted greater disability, but greater pain-contingent resting (i.e., reporting the use of sedentary behaviors as a method of coping with pain) was the strongest disability predictor. Taken together, these data suggest that a biopsychosocial intervention in regard to CP/CPPS pain is warranted and that cognitive-behavioral variables such as catastrophizing have a robust relationship with CP/CPPS pain and patient adjustment.

Recently submitted data examining CP/CPPS Quality of life using a similar BPSM to that of Tripp et al. *(43)* examined the associations between demographic, pain, urinary, psychological, and environmental predictors in men with CP/CPPS *(90)*. In this study, demographics, urinary symptoms, depression, current pain, pain coping, catastrophizing, pain control, social support, and solicitous responses from a partner were used as predictors of the mental and physical components of QoL. Poorer physical QoL was predicted by worse urinary function and increased use of pain-contingent resting as a coping strategy. Furthermore, poorer mental QoL was predicted by greater pain catastrophizing (i.e., helplessness subscale) and lower perceptions of social support from family and friends. These latest data support a BPSM for QoL in CP/CPPS, suggesting that specific coping and environmental factors (i.e., catastrophizing, pain-contingent resting, social support) are significant in understanding CP/CPPS patient adjustment.

Catastrophizing is a particularly salient factor in the recent CP/CPPS data examining patient adjustment and has been identified as a robust detrimental factor in chronic pain patients (e.g., *(29,91)*). Catastrophizing is described as the tendency to magnify, ruminate, and feel helpless when thinking about painful sensations *(29,92)*. Catastrophizing can be interpreted as similar to Beck's cognitive theory of depression *(93)*, wherein patients are likely to perceive misattributed psychological or physical symptoms using habitualized information processing in ways that increase the likelihood that negative outcomes are expected as fact, not possibilities. It is important to act to reduce catastrophizing in patients experiencing pain because it is described

as cognitive processing that is consistent over time and without intervention is related to increased emotional distress *(29)*.

Considered together, the CP/CPPS data for pain, relationships, and QoL suggest that a BPSM of intervention is warranted. In particular, catastrophizing is offered as a particular target for therapeutic change based on its robust and reliable association of pain, disability, and QoL. An integrative BPSM of chronic pain must incorporate the mutual associations between physical, psychological, and environmental variables and the likely changes amongst these that occur over extended periods of time. Furthermore, a model of treatment that focuses only on one of these medical/interpersonal variables is arguably incomplete.

A COGNITIVE-BEHAVIOURAL SYMPTOM MANAGEMENT PROGRAM FOR CP/CPPS?

The general cognitive-behavioural therapy protocols have been adapted from the depression and anxiety literatures to address pain. In particular, pain appraisals and catastrophizing have been of particular therapeutic interest in such treatment models. A cognitive-behavioural therapy is not a replacement for ongoing biomedical efforts to ease patient symptoms, but it should be considered a significant adjunct in such treatment efforts. This may be especially pertinent when the patient's pain has a history of severity and persistence. Cognitive-behavioural approaches are designed to assist patients in developing coping skills to manage their physical symptoms and the accompanying distress necessitated from persistent symptoms. Many pain specialists today suggest that persistent pain and its related symptoms should be conceptualized as a chronic disease such as diabetes because it is anticipated that without a cure, patients report better QoL when engaged in symptom self-management.

The cognitive-behavioural model of chronic pain has been systematically evaluated and is an efficacious treatment for pain. For example, outcome studies of cognitive-behavioral treatment (CBT) for chronic pain show reductions in patients' pain, distress, pain behavior, and improvements in activities of daily living. Treatment that has focused on decreasing negative thinking and emotional responses to pain, decreased perceptions of disability, and increased orientation toward self-management are predictive of favorable treatment outcomes *(94,95)*. The CBT model states that different cognitive factors are essential components to patient adjustment but that coping responses/behavior are equally involved in patient adjustment. It is the interaction between thoughts and behavioral outcomes that is a point of explicit patient education and skill development. CBT models suggest that individuals are not passive in their interpretation and response to the world around them. Indeed, individuals learn to respond to stressful and positive situations through learned experiences that help shape their individualized schema (i.e., organized internal cognitive representations of personal knowledge that acts in a heuristic manner) *(93)*.

There are several common characteristics of CBT programs. CBT programs are usually problem oriented, extensively make use self-management skills in regard to monitoring and challenging dysfunctional and unsupported thinking, teach communication skills, make use of homework-based exercises, promote activity engagement, and prepare patients to anticipate setbacks in plying these new skills *(93,96,97)*. These therapeutic tasks are used as guides to help patients identify and modify significant problem areas they may be experiencing in adjusting to persistent symptoms, such as

the case of chronic pain. The CBT framework is malleable and can be used in settings of one-to-one engagement or group settings as is often found in multidisciplinary pain management programs.

Our research site, which is supported by the National Institutes of Health, has developed and is currently examining a novel symptom management program for CP/CPPS. This Cognitive Behavioural-Symptom Management Program (CB-SMP) is unique to CP/CPPS management because it is based on current empiric findings of CP/CPPS research and reviews *(43,89,90)*. The use of current data to guide targeting of particular variables associated with patient adjustment makes the CB-SMP "specific" to the pain-related fears and cognitions of the CP/CPPS population. What also makes the CB-SMP novel is that it is being examined with trained program providers (e.g., clinical urology nurses) using a patient workbook to insure quality assurance of program delivery. The patient workbook provides focused readings and session-by-session homework tasks over the course of an 8-week schedule and patients are instructed on the use of particular tool referred to as the "Reaction Record" (see Table 1-the columns illustrated in this table detail the particular queries made of the patient, patients are asked to record their responses to these in separate sections below these columns). The Reaction Record directly guides patients in identifying negative thoughts associated with pain, distress, and/or negative interpersonal appraisals by asking them to complete each column going left to right based on a particular situation they found to be emotionally or physically difficult. The Reaction Record is also the mechanism by which patients are guided in deliberating, recording, and engaging in positive coping choices.

The content of the CB-SMP sessions are workbook defined and lead by a session agenda. The initial session is an introduction to the program requirements, the program rationale, and the value of the CBT approach. In sessions 2–3, patients are actively instructed on the use of the Reaction Record in self-identifying and modifying catastrophic cognition and understanding how such thinking is associated with greater negative affect, little supportive evidence of such thinking in their environment, and how it can lead to poor choices in behavioral coping (i.e., becoming sedentary and losing social activity that was once enjoyable). During sessions 4–6, patients identify and modify deficits in social support by practicing self-assertion communication exercises with their nurse and then later with significant others in their lives. Listening skills are also introduced, so patients can learn to identify when their symptoms may be interfering or biasing the messages that others are trying to provide them with. Sessions 6–7 uses the Reaction Record tool to identify and modify illness-focused behavioral coping strategies and also to help reengage the patient in physical and social activities that they have abandoned. In the final of the 8 sessions, patients are instructed in ongoing problem solving and future self-management challenges following treatment. In summary, the CB-SMP is the first comprehensive attempt to target specific empirically supported biopsychosocial variables (i.e., catastrophizing, social support) for symptom improvement in CP/CPPS. It is suggested in the observed associations between symptoms such as pain, catastrophizing, social support, and QoL *(87,90)* that such treatment may also act to improve QoL in CP/CPPS sufferers.

The goals of the CB-SMP are similar in nature to those of most CBT approaches. The four major goals of the CB-SMP are to (i) initiate a *sense of hope* by helping patients establish the belief that the self-management of their symptoms can shift from a state of being devastating to manageable; (ii) promote *self-efficacy* in symptoms management

Table 1
Reaction Record

*When you notice **Pain** or **mood getting worse** ask yourself, " What is going through my mind at this moment?"*

Date/ time	**Problem situation**:	**Automatic Thoughts**:	**Emotion(s)**:	**REACTION**:	**Adaptive Coping:**
	What actual event led up to this event? (e.g., attempt to do some activity, movement you are afraid of, a verbal fight . . . etc). What upsetting physical symptoms do you recall?	What are you saying to yourself about this problem situation? (e.g., This will never change. I can't do it. If I do that it will make me worse. These symptoms are ruining my life.) What were your thoughts or picture in your mind at this time? How much did you believe each thought at that time? Rate each from ***0–100%***	What emotion(s) did you feel at that time (e.g., sad, angry, anxious, happy)? How intense did you feel each of the emotions listed? Rate each from ***0–100%***	What did you actually do following your thoughts and emotion(s)? How did you react? (e.g., resting, giving up attempt, argued, verbal confrontation, tried to ignore it, etc.)	Doing something different? Ask: "What is the evidence that the automatic thought is true or not true for me?" "If I keep reacting like this in the future, what benefit will I get from it?" "If I had a good friend _____ in this situation what would I tell them to do?" Challenge Automatic Thoughts column and Reaction column! Then ***go back*** and ***re-rate emotions*** if you were to use these new thoughts to replace old ones you had.

through the acquisition of new thinking and new wellness-focused behavioral coping strategies. New strategies such as non-catastrophic thinking, positive self-coping statements, and mild–moderate exercise (i.e., walking program) are suggested and evaluated by patients. The practice of new skills allows patients to stop being reactive in the face of their symptoms providing a sense of mastery; (iii) Break established patterns of *schema-based automatic thinking*. In the CB-SMP, the practice of self-management skills takes direct aim at breaking patterns of catastrophic thinking with the Reaction Record tool. The use of the Reaction Record allows patients to build confidence that they have the ability to evoke change in the management of their condition (iv) *Facilitate long-term adjustment* by helping patients anticipate problems with their attempts at self-management. The closing session of the CB-SMP provides explicit education and discussion about self-management into the future. Patients are encouraged to practice their new skills on a regular basis, not just in times of perceived need.

THE CHALLENGE FOR MEN IN THERAPY

When considering adjunctive therapy-based treatment for symptom management in CP/CPPS, there are questions related to the potential pitfalls of engaging men in a process that they have been historically reluctant to participate. There are specific affective and behavioral characteristics of being male that influence men individually as well as in their relationships. "Manhood", if I can use that term, is a unique and complicated process often misunderstood by the therapeutic community. The question of what underlies the development of the stereotypical male perception of the world usually is addressed by the effects of gender role conditioning. Gender roles are not biological but a socially mediated phenomenon of development that are associated with powerful expectational sets for emotions and distress designed to guide behavior for men. Clearly, habitual ways of responding to and interpreting life events are as heavily influenced by gender learning for men as it is for women.

Goldberg *(98–100)* is regarded as one of the original writers to provide insights into the male socialization experience and to stand it apart from the female experience. In particular, Goldberg warned that the tremendous societal pressure experienced by men to project a masculine image to others was in direct contradiction to the inner needs of many men. Men had particular difficulty with interpersonal needs that were considered and described by the larger North American society as feminine in nature. Thus, the seeking of emotional help for distress is a challenge for most men, one that may be associated with feelings of weakness, failure, or anger. Indeed, part of acting and being male is to consciously or unconsciously deny the existence of needing assistance and to dissociate from the natural human feelings of fearfulness, sadness, and their need for help which many men interpret as a form of dependency. Instead of acknowledging feelings associated with such dependency, males typically value logic and rational thought, both valued as masculine traits to aspire to. Unfortunately, one emotional response men have been socially given permission to experience and express is anger. This unbalanced emotional/coping spectrum for men can be very problematic when the situation they are facing involves changes in their physical being which influences their overall QoL as is the case in CP/CPPS.

Therapy for men is similar to that for women in several ways and can lead to insights and the development of new methods of coping for the future. In expressing their emotions and trying to understand their root causes (referred to as automatic

cognitions) therapeutic treatment can assist men in managing distress. Given their social gender conditioning, most men find it particularly challenging to be in a position of needing and seeking assistance. Given the multiple issues in engaging men in therapy, strategies must be considered to reduce the inherent barriers. For example, developing the awareness necessary for the recognition of their emotions is a challenge because many men will be reluctant to engage in a process that can be interpreted as "touchy-feely." It is suggested that a "male" approach to therapeutic engagement that concentrates on activities, setting goals, using lists and diagrams, the use of homework, and the clear setting of a joint agenda will aid in fostering a therapeutic engagement likely to benefit the patient.

There are several suggested steps in the therapeutic process with men that are suggested as useful in developing patient engagement and enhanced symptom management skill development. One of the first tasks is to normalize the process of seeking help and reassuring men that they have made a positive decision that will help them feel better about how they manage their symptoms and then how they can improve their overall QoL for themselves and their family. A second step is to engage the male patient within a set structure, showing men how they are to proceed in a step-like manner where they have responsibilities of the therapeutic program to complete. Here, it is also important to reassure men that failing any homework attempt is acceptable and that the process of failing is part of the formula for success along with "getting back on the horse." This type of reassurance and positive feedback allows the men to realize the pressure placed upon them by the unrealistic expectation that they cannot receive help for their distress and understanding that distress at an intrapersonal level. As the symptom management program proceeds it is important to emphasis and reinforce the positive effects of internalized changes in awareness, self-coping statements, positive communication of emotional needs to others close to them (i.e., significant others, family, friends), and behavioral changes in their previous responses to distressing situations that may involve pain, sadness, or frustration. Finally, the therapeutic relationship is a model for men in therapy to safely learn to communicate and explore their distress in a non-threatening situation. This can be especially important in CP/CPPS because there is the frustration of pain and disability related to pain as well as the sensitive issues of relations strain and mood regulation, both which are heavily impacted by symptoms like pain.

CONCLUDING COMMENTS

The research reviewed and suggestions proposed in this chapter are designed to help emphasize that *variability* in patients' responses to pain and biomedical treatment is a likely outcome. When considering that pain is a very personal experience influenced by the threat value of the situation, an individual's prior history with pain, their cognitive appraisals and behavioural coping responses (i.e., catastrophizing), the social milieu in which the pain occurs (i.e., social support) and the course of the pain pathophysiology, a wide range of individual differences in responses to pain, disability, and QoL are predictable. In the case of males, particular coping strategies and emotional regulation may have specific impact on poorer QoL through the creation of intrapersonal and interpersonal stress.

CP/CPPS is only recently being recognized as a chronic pain condition as was suggested a decade ago *(9)* and should be examined in light of the theory and research

related to the physiology of pain and the psychological suffering that such conditions manifest. In this sense, the persistent pain found in CP/CPPS should not be viewed from a restrictive biomedical model because pain is not a purely physical phenomenon but rather a complex physical, emotional, and interpersonal fusion, where the negative outcomes are suggested to advance over time if left unchecked.

Using a BPSM to conceptualize CP/CPPS symptoms and patient adjustment, physical and psychosocial variables should be equally targeted for therapeutic improvement because it is likely the interaction between such variables that creates distressing subjective experiences for patients *(50)*. As reviewed here, there is an obvious association between CP/CPPS psychological and social variables that predict greater pain, disability, and poor QoL *(43,89,90)*. It is suggested that if treatment is to proceed in CP/CPPS targeting only the biomedical aspects and ignoring the psychological and social facets, then this model is inevitably unfinished.

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15 The Stanford Protocol for Prostatitis and Chronic Pelvic Pain Syndromes

David Wise, PhD

Summary

The Stanford Protocol, originally called the Wise–Anderson Protocol, proposes that a chronically contracted pelvic floor rather than inflammation or infection may be the cause of pelvic pain, urinary frequency, and sexual pain in men who have had no evidence of infection and no anatomical abnormality. This neuromuscular disorder is amenable to a behavioral, non-drug, and non-surgical intervention aimed at rehabilitating a hypertonic pelvic floor musculature. The Stanford Protocol involves training in Paradoxical Relaxation to release tension at specific trigger points and modify the patient's tendency to unconsciously and habitually tighten the pelvis.

Key Words: Stanford protocol; Wise-Anderson protocol; Hypertonic pelvic floor; Paradoxical relaxation; Dysfunctional protective guarding; Trigger point release; Physical therapy.

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DYSFUNCTIONAL PROTECTIVE GUARDING IS AT THE HEART OF CHRONIC PELVIC PAIN SYNDROMES

The Stanford Protocol is a name that was given by an internet support/chat group of patients suffering from different varieties of pelvic pain, to a protocol originally called the Wise–Anderson Protocol. It was developed in the Urology department at Stanford University in the mid 1990s out of the meeting of David Wise, a psychologist who had been able to resolve his condition of long time pelvic pain and neurourologist Rodney

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Anderson who was a professor of urology at Stanford and the director of the Stanford Pelvic Pain Clinic.

The Stanford Protocol represents a significant paradigm shift from the concept of conventional urology. It proposed that men presenting with pelvic pain, urinary frequency, and sexual pain who had no evidence of infection and no anatomical abnormality were not suffering as the result of prostate inflammation or infection but rather from a chronically contracted pelvic floor. This paradigm shift proposes that what is commonly diagnosed as abacterial or nonbacterial prostatitis is in fact a neuromuscular disorder most amenable to a behavioral, non-drug, and non-surgical intervention aimed at rehabilitating a hypertonic pelvic floor musculature. The paradigm of the Stanford Protocol stands in stark contrast to the more commonly held views that pelvic pain is the result of prostate-related disease, occult prostate bacteria, autoimmune disease, or compressed pelvic nerves.

Also, in contrast to the tepid medical reception of the Stanford Protocol, patients' response has been overwhelmingly enthusiastic. Peer-reviewed studies in the *Journal of Urology* documented a remarkable effectiveness of the protocol. The paradigm of the Stanford Protocol proposes that pelvic pain and urinary and sexual dysfunction involves the overuse of the human reflex to tighten the genitals, rectum, and contents of the pelvis in response to anxiety, pain, or trauma by chronically contracting the pelvic muscles. This tendency becomes exaggerated in predisposed individuals, particularly those with a tendency toward anxiety who respond to stress by habitually and unconsciously tightening their pelvic floor. Such a tendency is invisible. No one can see it. Usually, the person who has such a tendency is unaware of it. And the consequences of this tendency are also invisible to conventional medical technology. Complaints of pelvic discomfort, pain, sexual, and urinary dysfunction distinguish this disorder.

This state of chronic pelvic floor muscle hypertonicity creates pain-referring trigger points in and around the pelvis, and according to the Stanford Protocol creates an inhospitable environment for the nerves, muscles, blood vessels, and structures within the pelvic basin. This results in a self-feeding cycle, a short circuit of tension, anxiety, and pain, which has been previously unrecognized and untreated.

Most physicians neither appreciate nor understand the havoc that chronic tension plays in the pelvic floor. The Stanford Protocol proposes that the vast majority of male pelvic pain represents a functional and not a structural disorder. Pelvic pain involves the same havoc that chronic neck and shoulder tension plays in a headache, chronic back tension plays in low back pain, or chronic jaw clenching plays in temperomandibular disorder. There can be psychological, physical, or social triggers to the chronic tightening of the pelvic floor. The Stanford paradigm proposes that once this cycle of tension, anxiety, and pain begins, it tends to have a life of its own, and carries on even when the initiating triggers have disappeared.

The purpose of the Stanford Protocol is to break this tension, anxiety, pain cycle and to help patients prevent its reoccurrence. The methodology is low tech. The Stanford Protocol is a behavioral treatment that ultimately eschews the use of medication. The aim is to get patients off of all drugs and to end patient dependency on professional help. The responsibility for the success of the treatment is largely up to the patient's compliance with the protocol. Patients who look for a quick external fix to their condition tend to lack the motivation that the Stanford Protocol demands. Such individuals tend not to be good candidates for our protocol.

The problem in the great quest to restore the pelvis to a relaxed and symptom-free state is that pain and tension and trigger point activity in the pelvis turns out to be intimately tied up with the emotional reactivity and autonomic arousal. They feed each other. Anxiety is the gasoline on the fire of pelvic pain. This is also why placebo is so influential in this condition. This intimate tie-up with autonomic arousal and pelvic pain has never been effectively addressed in treatment and is essential to any effective treatment.

In a study published in the July 2005 *Journal of Urology*, we studied 138 patients who were referred usually by physicians who could no longer help these patients because they had failed all conventional therapy. We were the court of last resort. After that treatment, using the Stanford Protocol, 72% of these refractory patients report that they had marked or moderate improvements in their symptoms as reported on the Global Response Assessment. *These responses reported as marked and moderate improvements by patients were commensurate with appreciable (10.5% decrease in marked and a 6.5% decrease in moderate) decreases in NIH-CPSI scores*.

Paradoxical Relaxation addresses and seeks to reverse the dysfunctional reflex to guard against pelvic pain and the fear associated with it. The *reflexive reaction to tighten the pelvis in response to pain paradoxically exacerbates it*. Pain is a stimulus that triggers fight or flight. Pain does not reflexively trigger repose and rest, which is in fact what Paradoxical Relaxation requires patients to do. Accepting tension as a way to relax it, is counter-intuitive. Paradoxically, this counter-intuitive strategy that instructs patients to accept pelvic tension as a way of relaxing is why this method of relaxation is called Paradoxical Relaxation.

This *dysfunctional protective guarding* exists in a number of other functional somatic disorders. They include tension headache, temperomandibular disorder, low back pain, non-cardiac chest pain, and idiopathic dyspepsia among others.

The central strategy of Paradoxical Relaxation comes from the insight that *accepting tension relaxes it*. In Paradoxical Relaxation, the emphasis is on tension and not on pain even though pain is usually perceived peripherally during the relaxation training.

Paradoxical Relaxation is not new. The major insights of this therapeutic strategy derive from the world's oldest wisdom traditions and practices that focus on quieting the mind and body, and from the methodology of my teacher Edmund Jacobson who developed the technique of progressive relaxation.

The paradox of Paradoxical Relaxation can be expressed in the following ways: *that accepting tension relaxes it, that accepting what is, is the fastest way to change it, that what we resist persists, that the requisite for changing something is first accepting it as it is, on its own terms*. This happens to apply to stubborn pelvic muscle tension. Remarkably, this insight, when practiced regularly in a pelvic floor reduced of trigger points, has the potential to allow patients to dissolve pelvic pain.

Accepting tension is *both counter-intuitive and functional* in terms of relaxing stubborn tension associated with functional somatic disorders mentioned above. Paradoxical Relaxation is a modern day method to implement this perennial wisdom for ordinary people who have pelvic pain.

Here are some notable aspects of the trigger point release protocol we use.

The other methodology used in the Stanford Protocol is trigger point release-oriented physical therapy. Trigger points that refer pelvic pain exist both inside and outside the pelvic floor. The most common trigger points in male pelvic pain are found in the anterior levator ani, the obturator internus, adductors, and surprisingly in the quadratus

lumborum and the psoas. There tend to be specific trigger points related to specific pelvic pain symptoms. Trigger points tend to be found anteriorly in patients with more urinary symptoms and posteriorly in patients complaining of rectal pain. We use a method called pressure release on a trigger point, holding it for 30–90 seconds—this length of time, which is usually difficult for many therapists to routinely hold, is critical to the release of the trigger point. The Stanford Protocol rarely relies on trigger point injection, and then only with stubborn external trigger points and even then we never advise the use of botox in such injections. We never advise or practice the injection of internal trigger points.

Because the orientation of the Stanford Protocol is to teach patients to do trigger point release themselves, self-treated trigger point release is recommended to be done daily for many months until symptoms abate and then less frequently but regularly for a number of months. We generally discourage Kegel exercises and do not use pelvic floor biofeedback or electrical stimulation. Patients are taught external and internal trigger point self-treatment. We have found that patients can do the majority of the Stanford Protocol physical therapy themselves once they are shown how to do it. We continue to develop an internal wand, which we sometimes prescribe for patients when a patient has no partner or other resources to work with the internal trigger points at home. This has to be used carefully and only after the patient has been thoroughly instructed in its use. In the Stanford Protocol, trigger point release is done concomitantly with Paradoxical Relaxation.

Both Paradoxical Relaxation and Stanford Protocol physical therapy aim to rehabilitate the patient's pelvic floor and to stop the habit of chronically tightening the pelvic muscles under stress. For most patients, each method is necessary but not sufficient in restoring the pelvis to a symptom-free state. The intrapelvic trigger point release we use aims to rehabilitate the pelvic muscles and allow them to relax. The focus of Paradoxical Relaxation is to allow a rehabilitated pelvis to profoundly relax and to support the healing mechanism of the body with respect to a chronically sore and contracted pelvic floor. Importantly, a central purpose of Paradoxical Relaxation is to modify the habit to unconsciously and habitually tighten the pelvis.

Generally, if patients do not learn to voluntarily and regularly relax the pelvic floor and reduce their own nervous system arousal, in the long term, manual physical therapy efforts at rehabilitating the pelvic floor tend to be short lived. Patients easily go back to the old habits that brought about the condition in the first place. A stressful hour in traffic or a fight with one's partner after the best of physical therapy session can easily reactivate the trigger points that the therapist has just deactivated. I have seen this with many patients and know it personally.

The format of the Stanford Protocol is unusual as it is done in a 6-day intensive immersion clinic involving some 30 h of treatment. At this clinic, patients are trained in Paradoxical Relaxation, receive daily physical therapy, are trained in self-administered internal and external trigger point release, specific stretches, and related physical therapy techniques. It is the goal of this clinic for the patients to be able to self-administer most of the protocol without reliance on additional treatment.

The Stanford Protocol represents a different paradigm from one in which a patient who feels he has no control over his symptoms comes to the doctor to be cured and submits himself passively for the remedy. Our aim is to make patients independent. It is our goal that patients trained in our protocol find themselves in a position to take care of and possibly resolve this condition themselves without dependency on drugs and others to do so for them.

III Genitourinary Disorders Affecting Only Women

16 Interstitial Cystitis

Kenneth M. Peters, MD
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Summary

Interstitial cystitis (IC) is a chronic pelvic pain syndrome. The key symptoms are urinary urgency, frequency, pelvic pain, bowel dysfunction, and vaginal pain in the abscence of other identifiable causes such as urinary tract infection, bladder cancer, or endometriosis. Treatment should be multifocal, not directed solely toward the bladder, and multimodal encompassing stress reduction, psychological support, dietary/behavioral therapy, pelvic floor and physical therapy, pharmacologic therapy and neuromodulation.

Key Words: interstitial cystitis; pelvic pain; neuromodulation; treatment.

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INTRODUCTION

Interstitial cystitis (IC) was first described more than 90 years ago *(1)* as a distinct ulcer seen in the bladder on cystoscopy. The presentation may be variable; however, the key symptoms are urinary frequency, urgency, and pelvic pain *(2)*. In the recent past, the definition has been expanded to include patients with ulcers and also those with irritative symptoms and glomerulations (petechial hemorrhages) seen on bladder over distension under an anesthetic. More recently, the need for a bladder hydrodistension

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to aid in the diagnosis has come into question *(3,4)* and the definition has been further broadened to include patients with only symptoms of urinary urgency, frequency and pelvic pain, who had identifiable causes ruled-out such as urinary tract infections, bladder cancer, and endometriosis. Thus, the term "interstitial cystitis" is a misnomer, because no pathologic evidence of inflammation needs to be found. Changing the terminology to reflect symptoms rather than a pathologic process may be helpful in expanding treatment options. Several proposals have been suggested including painful bladder syndrome (PBS) or chronic pelvic pain syndrome (CPPS). Adopting a more general term such as CPPS may help physicians, other health care providers, and patients to move away from focusing on the bladder to treat IC, and begin to look at this syndrome in terms of being a pelvic disorder. The following chapter is designed to discuss the diagnosis and management of IC including CPPS in this terminology.

Regardless of the terminology used, the management of IC remains challenging for health care providers and patients. Sixty percent of IC sufferers complain of pain with sexual intercourse, many so severe they abstain altogether *(5–7)*. Most IC patients have been treated with antibiotics for recurrent infections, although a review of medical records usually fails to document infections. IC patients often have other associated disorders such as fibromyalgia, irritable bowel symptoms, pelvic floor dysfunction, and migraine headaches. Many IC patients have seasonal allergies and sensitivities to medications and foods *(8)*. Undiagnosed IC patients are often managed for years without directed therapy and will seek evaluation from many different physicians to help determine the cause and an effective treatment for their symptoms. Patients with IC have been told that their symptoms are "in their head and that there is nothing wrong with them." Often, IC patients have been counseled to seek psychiatric help for their disease, and many patients suffer unduly until a diagnosis is made. When a patient is found to have IC, justifying the symptoms by determining a diagnosis is often therapeutic. Once the diagnosis is made, directed therapy can be initiated for this syndrome. The impact of IC on a patient cannot be underestimated. IC patients had lower quality of life scores on questionnaires than patients on dialysis. Fifty percent of IC patients are unable to work full time. On average, $170 million per year is spent for medical care of IC. Combining lost wages and medical expenses, the economic impact of IC has been estimated to be $1.7 billion per year *(5)*.

Until recently, IC was believed to be a disease predominantly of women; however, more men are now being diagnosed with this disease. Men presenting with symptoms of genital pain, perineal pain, frequency, or dysuria are often labeled as having chronic, abacterial prostatitis. In fact, many of these men have characteristic findings of IC upon cystoscopy and hydrodistension and will respond to standard IC therapies *(9–12)*. IC is more prevalent in men than previously thought, and it is imperative that the health care provider has a high index of suspicion for IC in the man with chronic prostatitis symptoms.

The cause of IC is still unknown despite a century of study. The difficulty with IC is that it is a diagnosis of exclusion, and there are no specific objective tests to determine whether a person has IC or to monitor disease progression. There is hope that a marker for the disease may be available in the future. This marker is called antiproliferative protein factor (APF) and appears present in the majority of IC patients and minimally present in a control population *(13)*. For one to diagnose a patient with IC, the disease must be in the health care provider's differential diagnosis.

INITIAL PRESENTATION OF IC AND DIFFERENTIAL DIAGNOSIS

The typical IC patient presents with complaints of urinary frequency, nocturia, pelvic pain, low back pain, dyspareunia, and small voided volumes. These symptoms may wax and wane, but rarely will resolve completely. It is striking in the IC population that many patients can recall the exact time their symptoms began. IC should be considered a syndrome, and not all patients with IC will have all the symptoms associated with this disease. It is appropriate to characterize the type and degree of symptoms, the duration of the symptoms, and to determine whether a specific event led to their onset. There may be an association of IC with documented urinary tract infections or previous pelvic or bladder surgery. It is imperative that bladder cancer is ruled out by an evaluation of the upper urinary tract, bladder (cystoscopy), and urine cytology for any patients with hematuria and irritative voiding symptoms. A history of back pain or previous bladder or pelvic surgery may lead one to suspect a neurological cause for the symptoms. Obtaining a complete list of medical problems including diabetes, irritable bowel syndrome (IBS), neurological diseases, and malignancies is important. Assessing whether the patient has received therapies that may affect the bladder, such as therapeutic radiation or chemotherapies (i.e., Cytoxan), will aid the clinician in determining the cause of their bladder symptoms.

In premenopausal women, endometriosis needs to be in the differential diagnosis. If endometriosis is suspected, an appropriate evaluation, which may include hormonal manipulation or laparoscopy, should be considered. Dietary factors such as the amount of caffeine, alcohol, and acidic food consumption should be recorded, along with their effect on bladder symptoms.

Recognizing IC

The primary care physician is often the first to see patients with complaints of urinary frequency, urgency, and pain and has an important role in identifying patients who may suffer from IC. In addition, the primary care physician may begin education regarding this disease, initiate behavioral therapy, and secure the appropriate urological referral. Even before the diagnosis of IC is made, the primary care physician can initiate behavioral therapy that may often improve the symptoms of an irritative bladder. Many IC patients are sensitive to various food items *(14)*. Caffeine and alcohol should be removed from the diet, along with any other foods, such as tomatoes or citrus, which may worsen their bladder symptoms (Table 1). Calcium glycerophosphate (Prelief®) is an over-the-counter food supplement that neutralizes the acid in foods, and many patients believe this helps their IC symptoms, although no supporting clinical trials have been published *(15)*. Most patients with irritative voiding symptoms dehydrate themselves in the hope that they will void less. In IC, the protective barrier of the bladder is likely compromised, and this may allow the irritative solutes in the urine, such as potassium, to infiltrate the detrusor muscle, causing bladder irritation and nerve upregulation. Thus, patients who may have IC should be encouraged to increase their water intake, which will dilute the urine and cause less bladder irritation. Stress has been shown to worsen the symptoms of IC, and stress reduction may help alleviate pain, urgency, and frequency associated with IC *(16)*. Bladder-specific antibiotics and anticholinergics are the usual initial course of therapy. If the symptoms persist after a course of antibiotics or a urine culture fails to document an infection, IC should be considered. Finally, the primary care physician can initiate pain relief with appropriate

Table 1
Dietary Guidelines for Interstitial Cystitis

Food Category	*Foods Allowed*	*Foods to Avoid*
Fruits	Blueberries, pears, melons (no cantaloupe)	All other fruits or juices
Vegetables	Potatoes, homegrown tomoatoes, most vegetables	Avoid fava beans, lima beans,onions, rhubarb, tofu, store-bought tomatoes
Milk/Dairy	White chocolate, cottage cheese, milk, American cheese	Aged cheeses, sour cream, yogurt, chocolate
Carbohydrates	Pasta, rice, most breads	Avoid rye and sourdough breads
Meats/Fish	Poultry, fish, meats other than those listed under "foods to avoid"	Aged, canned, cured, processed and smoked meats and fish; anchovies, chicken livers, meats that contain nitrates or nitrites
Nuts	Almonds, cashews, pine nuts	Most other nuts
Beverages	Bottled/spring water, decaffeinated acid-free coffee and tea; some herbal teas	Alcoholic beverages, carbonated drinks, regular coffee and tea, cranberry juice
Seasonings	Garlic and seasonings not listed under "foods to avoid"	Mayonaise, ketchup, mustard, miso, spicy foods (especially Chinese, Mexican, Indian and Thai foods)
Additives		Benzol alcohol, citric acid, monosodium glutamate, aspartame, saccharin, artificial colors or ingredients

analgesics and recommendations to use heat or cold to the sacral and suprapubic areas for pain relief.

Diagnosing IC

One often suspects IC based on history alone after ruling out other causes that can mimic the disease, such as documented bacterial cystitis, overactive bladder, endometriosis, bladder cancer, and urethral diverticulum. Unfortunately, there are no available urine or serum markers for this disease, although several promising markers are under investigation *(17–20)*. In 1987 and 1988, the National Institutes of Arthritis, Diabetes, Digestive and Kidney Diseases (NIDDK) held workshops on IC and developed a research definition for IC *(21)*. The NIDDK criteria were found to be far too restrictive to be used as a clinical diagnosis for IC *(22)*. IC is a syndrome that may present as mild irritative symptoms to severe symptoms refractory to all standard therapies. It is important to recognize IC early to initiate appropriate therapies that often lead to rapid early improvement in symptoms. A referral to a urologist specializing in IC is the first step in securing a diagnosis. A physical exam, including a thorough pelvic

and neurological exam, should be performed. A postvoid residual should be obtained to rule out urinary retention. When performing a vaginal exam the anterior vaginal wall, including the urethra and bladder floor, should be carefully palpated. Urethral fullness, tenderness, or expression of pus may suggest a urethral diverticulum requiring further work-up. Often, in IC, tenderness to palpation of the anterior vaginal wall is noted at the level of the bladder trigone. Palpating the levator muscles may elicit tenderness, suggesting pelvic floor spasm. The patient's ability to contract and relax the pelvic floor muscles may suggest pelvic floor dysfunction. If the pelvic floor muscle complex is a source of pain, pelvic floor therapy should be considered. The degree of pelvic relaxation and prolapse should be determined. A rectal examination can rule out any rectal abnormalities or masses, and in men, the prostate should be palpated to assess for any palpable prostate disease. Urinalysis, urine culture, and cytology should be performed to exclude active infection or evidence of carcinoma in situ. Sterile pyuria should prompt urine TB cultures. If microscopic hematuria is present, a work-up, including upper-tract imaging, cystoscopy, and cytology, should be performed to rule out bladder cancer or stone disease *(23)*. A voiding diary with both fluid intake (amount and kind) and urine output, including voided volumes, daytime frequency, and nocturia, should be completed. The voiding diary allows one to determine the average voided volume and to document the amount of daytime frequency and nocturia. Validated IC questionnaires are available to monitor other IC symptoms, including pain *(24–26)*.

Sequential voiding diaries and symptom questionnaires allow one to determine the impact of various treatments for IC. A cystometrogram may be performed to rule out uninhibited contractions and to determine the functional bladder capacity. The usual cytometric finding in IC is a small capacity bladder of the sensory/urgency type without uninhibited bladder contractions. Once all medical reasons for the bladder symptoms are ruled out and anticholinergics have failed to relieve the symptoms, one may consider empiric treatment or proceed to other diagnostic tests.

The traditional test for the diagnosis of IC has been bladder hydrodistension under a general or regional anesthetic *(27,28)*. A hydrodistension may not only aid in the diagnosis of IC but also may improve symptoms. This procedure is performed in an operating room setting, where a complete cystoscopy is used to assess the urethra and bladder. The cystoscopy will help rule out bladder cancer or urethral diverticulum. After inspection of the bladder, the bladder is filled by gravity drainage at 80–100 cm/H20 pressure to its capacity. Upward pressure along each side of the urethra is often needed to maximally distend the bladder to prevent leakage around the cystoscope. The bladder is distended until no further water will run into the bladder, and this water is allowed to dwell for 2 min. The bladder is drained into a pitcher and the volume measured. Typically with IC, there is terminal hematuria seen when the bladder is drained. The average normal bladder capacity under an anesthetic is 1115 cc, and the average IC bladder capacity is 575 cc; however, in nonulcerative or early IC, the bladder capacity can be normal *(29)*. Upon reinspecting the bladder, the vast majority of patients will have glomerulations seen in all sectors of the bladder that are suggestive of IC. Approximately 15% of IC patients will have deep cracks or ulcers in their bladder called Hunner's ulcers, which are associated with more severe symptoms *(30)*. If ulcerative lesions are present, these should be biopsied and the entire involved area should be gently cauterized, which often leads to improvement in symptoms.

The vast majority of patients with the symptoms of IC will have the classic cystoscopic findings; unfortunately, these are not pathognomonic for IC and glomerulations

can be seen in the asymptomatic patient *(31)*. Thus, one must make a clinical decision based on symptoms and the cystoscopic findings when diagnosing IC. A bladder biopsy can be performed for pathological evaluation and to rule out bladder cancer. Unfortunately, there are no classic pathological findings associated with IC. Mast cells have been implicated in the pathogenesis of IC by releasing multiple substances that can lead to inflammation in the bladder, such as histamine, kinins, vasoactive peptides, and prostaglandins. Studies have not consistently shown an elevation in bladder mast cells in IC. The role that mast cells play in IC is currently under intense investigation *(32–36)*. Patients with IC should be informed that their symptoms may worsen for 2–3 weeks after a hydrodistension. Then they will usually return to their baseline or a marked improvement in symptoms may occur, which can last for many months. If an IC patient responds well to a hydrodistension, this can be repeated in the future as a part of their multimodal treatment.

A second test described to help diagnose IC is the potassium sensitivity test. This test is based on the hypothesis that there is increased epithelial permeability in the bladder of IC patients and that instilling a potassium solution in the bladder will provoke symptoms of urgency, frequency, and pain *(37–39)*. To perform this test, two solutions are placed in the bladder for 3–5 min. The first solution is 45 cc of sterile water and the second solution contains 400 mEq/L of KCL. After instilling the solution, the patient is asked whether it provokes symptoms on a scale of 0–5. If the patient does not react to water but states the KCL caused symptoms to increase two points or more on this scale, this is considered a positive test. Studies have shown that 70% of IC patients have a positive test, whereas 4% of a control population responded to potassium instillation. The pain caused by this test can be alleviated by rinsing the bladder with water and instilling heparin and lidocaine into the bladder. The benefit of the potassium sensitivity test is that it can be performed in an office setting, does not require cystoscopy, and may lead to a more rapid initiation of treatment for the IC. The downside is that it does not allow one to inspect the bladder for other causes of symptoms, it evokes acute pain in the non-anesthetized patient, and it does not provide the patient the opportunity to have a clinical improvement in symptoms from a hydrodistension. In addition, there is little evidence to suggest that a positive potassium sensitivity is specific to only IC because the test would also be positive in other disease states such as bacterial cystitis and bladder cancer.

TREATMENT OF IC

Validating a patient's symptoms by making a diagnosis of IC is usually therapeutic for the patient. Success in treating IC is facilitated by the patient's understanding that this is a chronic condition that typically has cycles of flared symptoms and "remissions." Empowering the patient with knowledge about the disease and treatment options, and including them in the treatment plan allows them to be proactive and participate in their care. A multimodal approach is the most effective means of treating IC. Behavioral therapies must be stressed such as fluid management, pelvic floor physical therapy/myofascial release, dietary restrictions, and relaxation therapy *(40)*. Many IC patients suffer from pelvic floor spasm, which causes pelvic pain, dyspareunia, and urinary hesitancy. Treatment by a therapist knowledgeable in myofascial release may markedly improve symptoms and often is the only treatment needed. If pelvic floor involvement is identified, it is reasonable to consider pelvic floor therapy as a first-line treatment before any invasive testing or medications are used.

Expanding our Diagnostic Perspective: the Role of Pelvic Floor Muscles

It is our experience that a large number of patients with voiding complaints and pelvic pain have pelvic floor dysfunction. This leads to dyspareunia, urinary hesitancy, urgency, bowel dysfunction, and low back pain. Pelvic floor dysfunction also explains why patients with IC often get worse during times of stress. Stress causes increased pelvic floor tension and worsening of symptoms. Often, physical therapy with a therapist specially trained in pelvic floor disorders can lead to a significant improvement in symptoms and may be the only treatment needed.

Muscles of the Pelvic Floor

The primary support for the pelvic organs comes from the levator ani (levators) muscles. The levators form a horizontal plane like a hammock under the vagina and urethra. Support of the bladder and bladder neck is provided by the anterior vaginal wall and the levator ani muscles. The levators are palpable just above the hymenal ring as lateral pressure is applied upon vaginal exam. The levators are divided into the coccygeal, iliococcygeal, and pubococcygeal muscle groups *(41)*. The coccygeus attaches to the spine of the ischium and fans out medially to attach to the coccyx and S5. The iliococcygeus goes from the lateral wall of the pelvis posterior to the ischial spine *(42)*. The pubococcygeus inserts bilaterally at the pubic ramus, and wraps around the bladder, urethra, vagina, and rectum *(43)* (Fig. 1).

It is important to remember that pelvic floor dysfunction may derive from the muscles, the nerves, or the connective tissue *(41)*. Innervation of the pelvic floor muscles is from the second, third, or fourth sacral nerve root through the pudendal nerve *(43)*, and direct innervation of the levator ani muscles is from the third or fourth sacral motor nerve root by the pudendal nerve. The majority of the nerve fibers in the levators are slow-twitch fibers that maintain constant tone, with more fast-twitch fibers in the perirurethral and perianal areas *(44)*. In addition, the pelvic floor is also supported by the endopelvic fascia, a group of tissues including collagen, elastin, smooth muscle, ligaments, blood vessels, and nerves *(42)*.

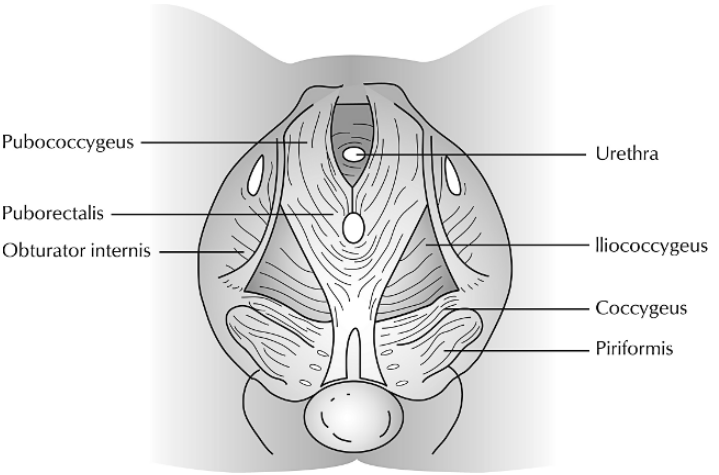

Fig. 1. Pelvic floor muscles.

Pelvic Pain

Myofascial pain and hypertonic pelvic floor dysfunction are present in as many as 85% of patients with IC and/or chronic pain syndromes. A noxious stimulus may trigger the release of nerve growth factor and substance P in the periphery causing the mast cells in the bladder to release pro-inflammatory substances causing neurogenic inflammation of the bladder wall. This can result in painful bladder symptoms (IC) and vulvar or vaginal pain. There may also be a viscero-muscular reflex resulting in the pelvic floor muscles being in a hypertonic contracted state. This hypertonic state results in decreased muscle function, increased myofascial pain, and myofascial trigger points. The pelvic floor muscles then become a source of pain even if the bladder is treated *(45)*. Researchers performed urodynamics in patients with IC or severe urgency and frequency and observed that pain episodes paralleled behavioral changes in the sphincter more than in the bladder. Pressure was applied to pelvic floor muscles, which elicited pain to the suprapubic area, perineum, rectum, and labia. Symptoms improved after neurostimulation or biofeedback *(46)*. Pelvic floor myofascial trigger points may underlie the pathophysiology of its progression. In addition, neural cross-talk may explain the interface of many chronic pelvic pain conditions including IC and IBS. Neural pathways coordinating smooth and striated muscle activity of the pelvic organs may respond to ongoing long-term stimulation by negatively impacting the non-irritated pelvic organs. This may lead to neurogenic inflammation and sensitization through the release of neurotrophic factors *(47)*.

Pelvic pain from levator ani myalgia may occur with sexual intercourse. Dyspareunia, vulvodynia, and vaginismus can be the result of contracted pelvic floor muscles. The resulting sexual dysfunction may affect the woman's self esteem and her relationship to her partner. It may also potentiate the pain-pelvic floor muscle contraction cycle. Usually, the woman with IC will also have an increase in her painful bladder symptoms of frequency, urgency, or pain with pelvic floor dysfunction *(48)*.

Clinical Evaluation for Pelvic Floor Dysfunction

First, a complete history should be taken including past surgeries, procedures, and medications that may impact the pelvic muscles or organs. Include an assessment for sexual dysfunction, history of any type of abuse, and psychosocial alterations in health. Note any traditional or complementary therapies that have been used to treat the PBS/CPP. A cotton swab test for vulvodynia should be done. This involves touching the vestibule with the cotton swab at the 2, 4, 6, 8, and 10 o'clock positions. Some clinicians choose to start at the thighs and move inward to the vestibule for a more complete assessment *(49)*. Response to touch is rated on a Visual Analog Scale (VAS) of 0–10 (no pain–worst pain ever).

A speculum exam, vaginal pH test (normal = 4.5), and wet mount slide should be done to check for vaginitis. Vaginal cultures for sexually transmitted infections (STIs) should be done if indicated. If atrophic vaginitis is present, hormone therapy may be adjusted. Vaginal examination should include assessment for vaginismus (note any tightening of the pubococcygeus at the introitus). Check for cervical motion tenderness (if cervix is intact), assess uterus and ovaries (if present), and note any bladder/urethral pain upon touch. To assess for levator pain, press your finger laterally on the levator at the ischial spines and then assess the levator muscles laterally, anteriorly and posteriorly. It is helpful to quantify any pain with a VAS. Normally, there would be no

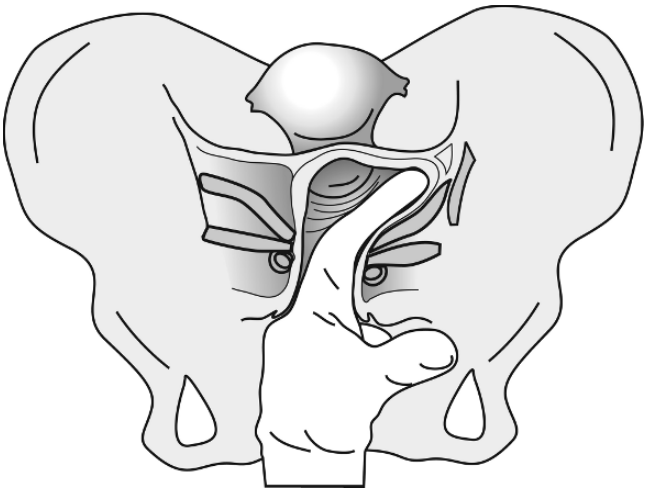

Fig. 2. Levator assessment.

pain. Assess both the right and the left sides, as there is often discordance in the pelvic floor tension bilaterally. It may be helpful to record the patient's pain responses and also the clinician's evaluation of muscle tension by palpation of the levators (Fig. 2).

Consideration must be given to other gynecologic or gastrointestinal disorders that may contribute to the pelvic pain. Appropriate referrals for evaluation and treatment should be made to gynecologists, gastroenterologists, psychologists, physical therapists, etc. Multidisciplinary approaches can be used to address the biological, psychosexual, psychosocial, and spiritual factors that contribute to the pain *(50)*.

Treatments for Pelvic Pain

Manual Therapies and Self-care

Physical therapy has been reported to be helpful in managing pelvic pain and relaxing the pelvic floor *(51)*; however, there are no published randomized controlled trials to support this in IC *(52)*. Weiss *(53)* utilized manual therapy for the pelvic floor trigger points and myofascial release in IC patients and found that 70% had marked or moderate improvement in symptoms after treatment. He found that pelvic floor therapy decreased the neurogenic triggers, decreased central nervous system sensitivity, and alleviated pain. With the patient in the lithotomy position, locate trigger points or tightness of the internal muscle groups with a 1-finger vaginal exam. These points are then treated with compressing, stretching, strumming at right angles to the affected muscle bundles or allowing the finger to glide between fibers to seek the direction of least resistance. When these techniques are applied in women, the tender areas in the urinary sphincter, periurethral tissues, and pubourethralis are compressed against the symphysis pubis, combined with lateral traction (Fig. 3). Use light pressure initially, and steadily increase as the patient tolerates, being mindful of not inducing a muscle spasm.

Repeat this stretching several times, then apply posterior traction in the vagina. The patient is then asked to contract the muscle while the examiner's finger is held fixed. This results in an isometric contraction against resistance. This stretching has a reflex inhibitory effect on muscle tension and results in greater relaxation and muscle length.

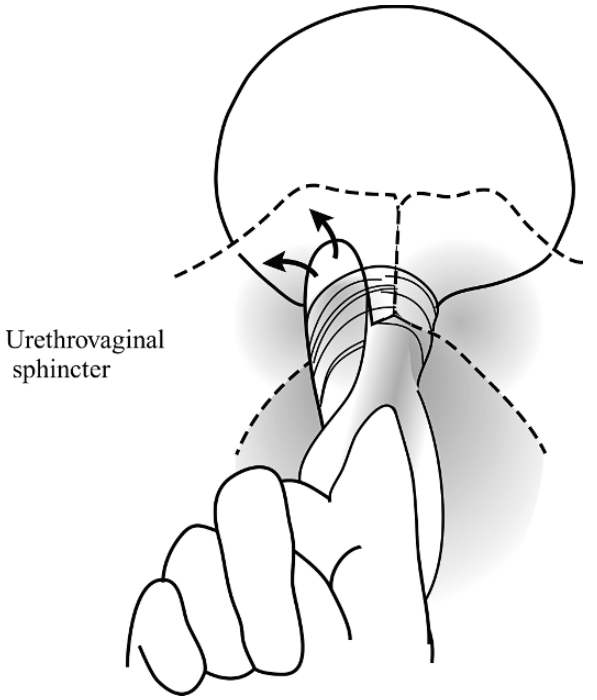

Fig. 3. Lateral stretching and compression of urinary sphincter.

The patient repeats this isometric contraction several times, which results in even more muscle elongation. The goal of these stretching exercises is to lengthen these anterior contracted muscles by decreasing periurethral tension, release trigger points in the levator muscles, re-educate the muscles to a normal range of motion, and improve patient awareness of muscle tension. Treatment should continue until tenderness and tightness have been minimized or disappeared, which requires 1–2 visits weekly for 8–12 weeks depending on the duration and severity of symptoms. As trigger points and muscle tension decrease in severity, the frequency of therapy is decreased. The patient is instructed in a home program consisting of pelvic muscle stretches and relaxation techniques.

Biofeedback. Significant pain improvement was found in a prospective study treating 16 patients with levator ani syndrome with biofeedback *(54)*. Electrical vaginal or rectal stimulation has been used with variable reported success in patients with high-tone pelvic floor dysfunction *(55)*. IC patients with long-term intravaginal or transcutaneous nerve stimulation with continuous, daily use eventually had a decrease in pain and frequency *(56)*.

Pharmacological Therapies

Various medications may be helpful including antidepressants (amitriptyline), anticonvulsants (gabapentin), and diazepam. Results are variable *(57)*. Botulinum Toxin A has been used in various muscle groups including the obturator internus and, levators and has been used in the vestibulum to treat vulvodynia. It inhibits the release of acetylcholine and the release of pain neurotransmitters such as substance P and histamine. The exact mechanism of action is unknown; yet, many theories are proposed in the

literature. Duration of action is 1–5 months, and there are few adverse events to date. It is not recommended as a first-line therapy *(58)*.

Once behavioral therapy and appropriate physical therapy is optimized, oral medication is indicated for the treatment for IC.

Oral medications. The only Food and Drug Administration (FDA)-approved oral therapy for IC is pentosan polysulfate sodium (Elmiron®). Pentosan polysulfate (PPS) is a glycosaminoglycan that binds tightly to the bladder mucosa. One theory of IC is that the bladder mucosa is "leaky," allowing the toxic substances in the urine to enter the bladder muscle, leading to inflammation and upregulation of nerve fibers. PPS may help rebuild the natural bladder barrier, leading to improvement in symptoms. PPS has been studied in several double-blind, placebo-controlled trials in the United States. In patients meeting the NIDDK criteria for IC, 28% of those receiving PPS at a dose of 100 mg three times per day for 3 months reported a 25% reduction in overall bladder symptoms compared with 13% of placebo-treated group *(59)*. An open-label physician usage study that enrolled 2809 patients from 1986 to 1996 demonstrated that 61% of patients on PPS for a minimum of 3 months developed improvement in pain or discomfort and this improvement was sustained while patients were taking PPS *(60)*. An IC patient must commit to taking PPS for 3–6 months before determining that it is ineffective, and in addition, if symptom improvement is achieved, PPS may need to be continued indefinitely to maintain the improvement. Unfortunately, PPS does not improve the symptoms of the majority of IC patients, and it is difficult to predict who will benefit from this therapy. A randomized prospective study comparing Pentosan Polysulfate and Cyclosporine A (CyA) for the treatment of IC reported in 2005 that CyA was superior to PPS in all clinical outcomes parameters. There was a significant reduction in frequency, increased bladder capacity and mean voided volume, a decrease in nocturia, and significantly improved VAS, O'Leary-Sant scores and global response assessments (75% for CyA; 19% for PPS, $P < 0.001$) *(61)*. PPS is a well-tolerated drug with 1–4% of patients complaining of alopecia (reversible upon discontinuation), gastrointestinal upset, headache, liver function abnormalities, or abdominal pain. PPS should not be given in conjunction with routine use of therapeutic doses of aspirin or nonsteroidal anti-inflammatories. PPS appears to help a subset of IC patients and has a good side-effect profile. PPS may be considered a first-line therapy for IC; however, because it may require several months before any clinical improvement is seen, it should not be used as a single agent for the treatment of IC.

Hydroxyzine is an antihistamine used primarily in the treatment of atopic dermatitis, urticaria, and allergic rhinitis. There is some evidence that mast cells may be involved in the pathogenesis of IC *(62)*. Hydroxyzine can reduce bladder mast cell degranulation, and anecdotal evidence suggests it may be effective in the treatment of IC *(62–65)*. This can be used in conjunction with PPS as part of a multmodal treatment regimen; however, a recent NIH-sponsored study showed that hydroxyzine and PPS were no better than placebo *(66)*. The main limitation of this study was that it was underpowered because of poor recruitment. Hydroxyzine may be more effective in IC patients who are found to have increased mast cells on bladder biopsy or those with seasonal allergies. Hydroxyzine is also sedative and in the short term often improves quality of sleep and decreases nocturia. With prolonged use, both daytime and nighttime IC symptoms may improve. Hydroxyzine should be started at a dose of 25 mg at night and titrated based on side effects to 75 mg per night. The dose may need to be increased during allergy season.

Antidepressants can be used alone or combined with PPS as an initial treatment regimen to aid in the treatment of IC *(67–69)*. Patients with chronic pain and sleep deprivation often develop clinical depression *(70)*. In addition, tricyclic antidepressants have been used for chronic pain disorders by increasing the pain threshold. Low-dose amitriptyline (10–150 mg) taken at night can be very effective in improving sleep and diminishing urinary frequency and bladder pain *(71,72)*. Patients should be cautioned that tricyclic antidepressants could cause weight gain and daytime sedation. The sedative side effects will usually diminish with continued usage. The dose should be slowly titrated to minimize symptoms. Some IC patients will benefit from serotonin uptake inhibitors, such as fluoxetine hydrochloride or sertraline hydrochloride. These are nonsedative and should be given once per morning. Although not FDA approved, it is reasonable to consider treating IC with antidepressants, particularly the tricyclic antidepressants.

Patients with IC often develop pelvic floor dysfunction, leading to tenderness of the pelvic floor muscles, urinary hesitancy, pelvic pain, and dyspareunia. Muscle relaxants, such a Valium or low-dose baclofen, may aid a subset of IC patients. Finally, patients should have "rescue" medications available to them to be used as needed for symptom flares. These may include urinary analgesics, such as Pyridium or Urised, anticholinergics, and pain medications. These medications can be used as needed by the patient to control symptom flares.

Intravesical Therapies for IC

Intravesical therapy for bladder symptoms has been used for more than 150 years. In 1855, Mercier used silver nitrate in bladder instillations with reported excellent results. Later, a group of 74 patients with IC were treated with intravesical silver nitrate under general anesthesia initially. The bladder was irrigated with a boric acid solution, and then 1:5000 solution of silver nitrate was instilled into the bladder, left for 3–4 min and drained. Side effects were burning and dysuria for 2–3 h. The treatments were repeated every other day, with increasing concentrations of silver nitrate (up to 1:100). Later treatments were given on an outpatient basis. Results were reported as "excellent" in 70% of patients at a mean response of 7.6 months *(73)*. Subsequent studies by other investigators have reported a 50–79% improvement *(74,75)*. Due to the caustic nature of silver nitrate, there is significant pelvic pain. A cystogram before instillation is necessary to exclude vesicoureteral reflux. Bladder biopsy along with instillation is contraindicated because of possible perivesical extravasation *(76)*.

Clorpactin WCS-90 (oxychlorosene sodium) has been used for 50 years for bladder symptoms. Various concentrations of clorpactin have been used, with results varying from a 50–80% improvement rate. A cystogram should be done to rule out reflux. Then under anesthesia, the bladder is distended for 2 min at 60–80 cm H_2O pressure and emptied. A solution of 0.4% Clorpactin is instilled in 150–200 ml amounts by gravity, left in for 2–3 min, and drained. This procedure is repeated until 1000 ml of solution has been instilled and drained. A normal saline irrigation is then done to the bladder and introitus *(77)*. The mechanism of action is still unknown, but it may work by desensitizing the nociceptive bladder nerve endings by releasing calcitonin gene-related peptide (CGRP) from the nociceptive terminals *(78)*. The problem with this therapy and silver nitrate therapy is the caustic, potential harmful nature of these substances to other tissues and organs *(79)*.

Dimethyl sulfoxide (DMSO) is a by-product of the wood pulp industry that was made in 1867. It was found to have anti-inflammatory, analgesic, and bacteriostatic properties. For more than 40 years, DMSO has been used to treat IC with overall positive short-term results. There is a response rate of 50–90%, with a 40% relapse rate. About half of these patients will respond to re-treatment with DMSO *(80)*. The mechanism of action of DMSO seems to be its ability to stimulate mast cell degeneration *(81)*, deplete substance P from the bladder wall, and cause nitric oxide release from the afferent nerves *(82)*. This leads to desensitization of the nociceptive pathways in the lower urinary tract *(83)*. Patients often experience a worsening of their symptoms initially, but with repeated treatments symptom-free intervals increased. DMSO is partially excreted through the alveoli and the subsequent garlic-like breath odor may last 6–24 h after treatment. DMSO is often administered as a 50% solution, or mixed with sodium bicarbonate, a steroid and heparin sulfate. A prophylactic antibiotic may be added or given orally. Approximately 50 ml of the solution is administered. The patient is asked to hold the solution for 30–60 min. This period of time may be increased with subsequent instillations done weekly for 6–8 weeks, then every other week, every third week, and every other month until symptoms are reduced. DMSO is the only FDA-approved intravesical therapy for PBS/IC in the United States *(79)*. Unfortunately, there have been no good placebo-controlled trials using DMSO because its unique garlic odor occurs in subjects treated with this instillation.

Intravesical bacillus Calmette-Guerin (BCG) has been used with varied success in treating IC symptoms. BCG is an attenuated strain of *Mycobacterium bovis*. It is used intravesically to treat recurrent or multifocal bladder cancer. In IC patients, 50 ml of a BCG solution is instilled into the bladder and retained for 2 h, with the patient changing position every 15 min. Six weekly instillations of BCG are given. In IC patients, a 21–60% response rate to BCG was noted in two studies *(84,85)*, whereas one study found no benefit from BCG treatment *(86)*. The mechanism of action of BCG is unclear. It has been suggested that BCG may alter the immune profile in IC as demonstrated by altered cytokine levels after BCG therapy *(87)*. Although there are no BCG-related complications in IC patients noted, complications in the oncology literature include gross hematuria, irritative voiding symptoms, and inflammatory bladder lesions "BCG granulomas."

Hyaluronic acid (HA) is a glycosaminoglycan component of the bladder surface. HA (Cystistat) has been used in treating bladder symptoms in IC patients. Instillations of 40 mg of HA were given weekly for 4 weeks, then monthly for 1–3 years. The response rates (partial or complete) at 3 months were 65–70%, with the complete response rate of 25% *(88,89)*. Studies done in the United States were not supportive of its use; thus, HA is not FDA approved for use in the United States—it is produced in Canada.

Heparin has also been instilled into the bladder of IC patients since the early 1960s *(90)*. There is virtually no systemic absorption of heparin when administered intravesically. Intravesical treatment with heparin and alkalinized lidocaine may be useful in acute IC flares with newly diagnosed patients *(91)*. Intravesical solutions comprise either 40,000 U heparin, 8 ml 1% lidocaine (80 mg) and 3 ml 8.4% sodium bicarbonate suspended in a volume of 15 ml fluid *or* the same solution with 8 ml of 2% lidocaine (160 mg) instead of the 1% lidocaine. After one instillation, significant improvement in pain was found with either therapy; however, the 2% lidocaine was more effective and lasted longer (at least 4 h) than the 1% lidocaine therapy. The

mechanism of action is may be related to immediate downregulation of the sensory nerves with the buffered lidocaine in addition to the glycosaminoglycan properties of the heparin on the bladder.

Capsaicin, the pungent ingredient in hot peppers, desensitizes C-fiber afferent neurons through its neurotoxic effects. Reports are varied on the successful use of capsaicin intravesically. Capsaicin (10 micromolar in 30 cc saline) given intravesically, held for 10 min, and instilled twice weekly for 1 month showed some improvement over time in frequency and nocturia, but not pain. Capsaicin does not cross the urothelium and its action is very specific to small diameter nociceptive afferents. The major side effect is the warm, burning sensation felt by the patient upon instillation *(92)*. Capsaicin is not clinically available.

To minimize the side effects of capsaicin, an analog, Resiniferatoxin (RTX) was tested. It is a vanilloid that is 100–10,000 times more potent than Capsaicin, yet without the severe burning effect. A small study of IC patients demonstrated a temporary significant reduction in pain, urgency and nocturia after one instillation of RTX. The RTX solution was 30 cc saline with 10 nM RTX in 0.1% ethanol that was instilled and held for 30 min, then drained *(93)*. Since then, a large prospective randomized clinical trial of RTX in various doses with 163 IC patients found that RTX did not improve pain, urgency, frequency, nocturia or overall symptoms over 12 weeks. Dose-dependent pain with instillation, bladder pain, and urgency occurred. Intravesical RTX was not effective in treating IC patients *(94)*.

In general, intravesical therapies can be used as an adjunct to the treatment of IC; unfortunately, there is not one agent that consistently and durably improves the symptoms of IC.

Surgery for IC

Radical surgery for IC is rarely indicated and should be used as a last resort. Augmenting the bladder or diverting the urine while leaving the bladder in place is often doomed to failure. Removing the bladder with urinary diversion may be effective in very select, end-stage cases. The key to success is patient selection. As this chapter outlines, in many people, the pain associated with IC may not originate from the bladder but from other sources such as the pelvic floor. It is imperative that before a cystectomy is considered, the bladder is carefully examined cystoscopically, along with operative hydrodistension under an anesthetic. The best outcomes are achieved in those with anesthetic bladder capacities of less than 300 cc or those with recurrent Hunner ulcer disease. In this carefully selected patient, a cystectomy with ileal loop or neobladder may result in a major improvement in quality of life. Because pain can become centralized, patients choosing this mode of therapy need to be aware that this may not resolve the pain associated with IC /CPPS *(95)*.

Endoscopic Resection or Fulguration of Ulcers

"Hunner's ulcers present in the bladder" was the classic description of ICs. They are diagnosed by cystoscopy and are found to be focal, inflamed, friable, erythematous patches within the bladder. Only 15–20 % of IC patients have ulcerative lesions within their bladder, and these patients will have more severe symptoms compared with the non-ulcerative patient. On cystoscopy, these lesions cannot be distinguished from bladder cancer, and a biopsy is required to rule-out cancer as a cause of the lesion. Although few IC patients have ulcers, treating these ulcers by completely eradicating

them can significantly improve symptoms. A loop resectoscope can be used to resect these lesions and the base cauterized. Alternatively, the involved areas can be gently cauterized with a bugbee, ball electrode, or neodymium: YAG laser. Most patients will have almost immediate relief in symptoms after cautery of the ulcers. Unfortunately, the ulcers often return and cautery can be repeated as needed.

Neuromodulation

IC was thought to be a disease of the bladder, but in many patients, it appears to be a syndrome involving the entire pelvic region with symptoms of urinary urgency, frequency, hesitancy, pelvic pain, bowel dysfunction, and vaginal discomfort. Chronic inflammation in a pelvic organ may lead to nerve upregulation to the spinal cord, affecting all pelvic structures. Various forms of neuromodulation may be helpful treatment modalities for IC.

Sacral Nerve Stimulation

Sacral nerve stimulation (SNS) shows promise for the treatment of refractory IC symptoms (InterStim® Medtronic, Inc). This technology is approved by the FDA for urinary urgency, frequency, urge incontinence, and idiopathic urinary retention. The benefit of SNS is that a test can be performed before placing a permanent implant. The response to the test is assessed, and if a patient experiences at least a 50% improvement in their symptoms and desires a permanent implant, the neurogenerator can be placed permanently in a subcutaneous pocket in the upper buttock. The device can be adjusted via an external programmer similar to a cardiac pacemaker, and the patient has his or her own external programmer to control the degree of stimulation. Early evidence suggested that temporary sacral nerve modulation may be very effective in treating refractory IC *(96,97)*. In addition, the University of Maryland found a decrease in antiproliferative factor and normalization of HB-EGF levels in patients with successful test stimulation *(98)*. Peters et al. reported sustained improvement in refractory IC subjects with permanent implantation and the success rate was increased with a staged test using a permanent lead, rather than a percutaneous office test *(99)*. Comiter reported that 17 of 25 patients with IC/PBS had a successful test stimulation and at a mean follow-up of 14 months, 16 of 17 maintained their improvement *(100)*. Finally, Peters et al. demonstrated that chronic SNS significantly improved pain levels and resulted in a reduction in chronic opiate use *(101)*. Further studies are needed to assess the utility of this technology for treating IC and to use these findings to study the pathophysiology of this disease.

Posterior Tibial Nerve Stimulation

Posterior tibial nerve stimulation (PTNS) had a positive effect in 39% of 33 patients with pelvic pain and voiding symptoms who were refractory to all other previous treatments *(102)*. They were treated for 12 weeks with PTNS following the Stoller technique. This technique stimulates the posterior tibial nerve with a 34-gauge needle placed bilaterally at SP-6. The needles are placed approximately 4 cm deep at a 30° angle cephalad. An adhesive grounding electrode is applied on each side near the medial calcaneus. Stimulation of the posterior tibial nerve is done by amplitude of 0.5–10 mA, with a fixed pulse width (200 μs) and frequency (20 Hz). Stimulation is applied for 30 min. The stimulation needs to be done on a weekly basis for 12 weeks,

and then an attempt to wean treatments to once per month is tried. Unfortunately, there are no sham studies done on PTNS for voiding dysfunction, so its use remains in question.

Management of Pain Associated with IC/CPPS

IC or CPPS may result in pain that makes it impossible to manage activities of daily living. The goal should be to treat IC syndrome in a multimodal approach including bladder-specific medications, physical therapy, psychological support, cautery of ulcers, neuromodulation, diet, stress reduction, etc. However, despite our best efforts, we may not be successful in controlling the pain. It is important not to assume that the pain is strictly from a bladder origin. Far too often we try to fix the organ; however, depending on the specialty evaluating the patient, the organ may change. The gynecologist may assume endometriosis or vulvodynia is the cause of the pain; the urologist sees the bladder as the cause and the gastroenterologist blames the colon. This "in the box" approach limits our ability to effectively manage patients with CPPS. The pain stems from the nervous system, and although each of the organs listed may be a component of the pain or a stimulus to start the pain cycle, a broader approach to controlling the pain is needed.

Unfortunately, even the best pain medications currently available are limited in their ability to manage chronic pain disorders. A meta-analysis of opiate use for chronic pain syndromes showed improvement ranging from 16 to 60%, with the average around 30% improvement *(103)*. A recent randomized controlled trial found gabapentin and morphine combined provided better analgesia at lower doses than either as a single agent *(104)*.

For patients suffering from severe pain, opiates should be considered and their use tailored based on the clinical response. If the treating physician is not comfortable prescribing opiates, then the patient should be referred to an appropriate pain clinic. The needs of these patients vary, and so the prescription for an analgesic must be individualized for that particular patient. Some may require intermittent opiates for a flare of symptoms and combination formulas may be prescribed (i.e. hydrocodone + acetominophen). The physician needs to monitor the use of these medications to be certain the patients do not exceed more than 4000 mg of acetaminophen per day. Patients requiring chronic narcotics may benefit from long-acting single agents such as morphine (Avinza®, MS-Contin®) or oxycondone (OxyContin®). In the past several years, treatment of chronic pain with Methadone has been proposed because of unique properties of this drug. Methadone is not only a strong opioid analgesic, but it has recently been found to inhibit *N*-methyl-D-aspartate (NMDA) receptors, thus giving methadone a unique dual action in managing pain *(105)*. Methadone is also titratable, inexpensive, and may have less tolerance issues than other drugs.

Regardless of the opiate chosen for pain control, patients need complete informed consent regarding chronic analgesic use including tolerance issues, drowsiness, driving and operating machinery, and agreement to a pain management contract to prevent misuse of the drug and protect both the patient and the health care provider.

CONCLUSIONS

The entire spectrum of IC/CPPS has changed. For years it was not correctly diagnosed and many patients were informed, "nothing was wrong with them and their symptoms must be imaginary." With increased education of patients and health

care providers, IC has been correctly diagnosed more often. Despite significant research, treatment directed only at the bladder has been disappointing. More recently, researchers have concluded that IC is a syndrome and the bladder may not be the sole source of symptoms. To aid in providing effective therapy, IC should be considered a CPPS, and as such, there is currently a trend to change the terminology to reflect this finding. It is important to evaluate the entire patient when directing therapy for their symptoms. A multimodal approach is the most effective means to control symptoms. This includes stress reduction, psychological support, dietary/behavioral therapy, pelvic floor and physical therapy, pharmacologic therapy, and neuromodulation. Patients presenting with symptoms of urinary urgency, frequency, pelvic pain, bowel dysfunction, and vaginal pain should have IC in the differential diagnosis and be treated by an interdisciplinary team. Early recognition and treatment of the syndrome usually results in more rapid control of symptoms. Recurrent urinary tract infection is the most common misdiagnosis of the IC patient. Urine cultures should be performed before initiating antibiotic therapy, and if cultures are negative, further evaluation for IC should be considered. The IC patient must partner with the treating physician and health care providers, be involved in directing therapy, and have reasonable expectations regarding symptom control. Continued research, comprehensive evaluation, and multimodal care will hopefully improve the quality of life of our patients with IC.

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17 Vulvodynia

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Summary

Vulvodynia is a condition exclusive to women and involves mostly burning, rawness, and itching of the external genitourinary tract in the absence of obvious concomitant clinical pathology. Vulvodynia often results in painful intercourse. Symptoms impact daily activities and negatively affect quality of life, often with significant economic and psychosocial costs to patients. There are many potential etiologies of vulvodynia. Uncontrolled studies have examined the use of oral, topical, and injection medical therapy as well as physical therapy. Surgical outcome for vestibulitis is favorable, but this should only be considered after all other treatment options have been exhausted.

Key Words: Vulvodynia; chronic vulvovaginal pain; vulva; sexual intercourse; tricyclic antidepressants; anticonvulsants; botulinum toxin; physical therapy; vestibulectomy; vestibulitis.

Contents

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INTRODUCTION

Vulvodynia is a term popularized by Tovell and Young in 1978 describing "pruritis, discomfort and pain that is often burning in nature where neither clinical nor laboratory evidence of a local or systemic disease can be discerned" *(1)*. In the past, it has been referred to as burning vulva syndrome, psychosomatic vulvovaginitis, vestibular adenitis, focal vulvitis, vulvar vestibulitis, dysesthetic vulvodynia, essential vulvodynia, or vulva pain syndrome *(2)*. It is a condition exclusive to women and involves mostly burning, rawness, and itching of the external genitourinary tract that often results in painful intercourse *(3)*. Vulvodynia rarely results in severe morbidity or mortality; rather, it causes symptoms of the lower genital, urinary, and gastrointestinal tracts that can impact a woman's daily activities and negatively affect her quality of life. Such symptoms often result in a significant economic and psychosocial cost to patients *(3–5)*. Women with vulvodynia report that their disorder affects their relationships, levels of stress and frustration, ability to perform household chores, and limits the kind of work they perform compared with women with other chronic vulvovaginal disorders (Jelovsek, in press). The majority of women visit two to six physicians while seeking treatment and a significant number report they do not trust their physician to effectively manage their pain *(3)*. Currently, no data exist on the economic impact of vulvodynia.

EPIDEMIOLOGY

Although chronic vulvovaginal symptoms are one of the most common reasons for visits to a gynecology clinic, epidemiologic studies of the incidence and prevalence of these conditions are rare and available population-based studies are limited. Most studies identify patients using various urban or web-based vulvodynia support groups and use non-validated questionnaires *(6–8)*. Additionally, most vulvar pain is recurrent with symptoms improving and worsening over time. Without prospective data, determining true remission rates is difficult. Approximately 16% of women will experience chronic vulvar pain at some point in their lifetime, with 5% experiencing this condition before age 25 years *(8)*. Over a 5-year period, 7% of women report vulvar soreness or pain whereas 4% report pain during intercourse *(6)*. One percent of new patients presenting to a genitourinary medicine clinic report vulvar vestibulitis *(9)*. A recent web-based survey demonstrated that 28% of women report a history of pain at the vulvar vestibule within a 6-month period; 3% report the pain lasting 3 or more months, and only 2% report pain lasting 3 months or longer *(10)*. Eighty-six percent of women frequenting electronic mail lists for a variety of vulvar pain disorders reported burning, rawness (71%), and painful intercourse (86%) *(3)*.

ETIOLOGY AND RISK FACTORS

Data on risk factors for chronic vulvar pain are few. Because dyspareunia is a common complaint from women with vulvodynia, many epidemiologic studies do not separate out pain with intercourse and chronic vulvovaginal pain *(11)*. Although up to a third of Swedish adolescents aged 12–26 years reported regular pain during and/or after intercourse, we do not know what proportion continue to have chronic pain. A large urban-based study demonstrated that the incidence of chronic vulvar pain was highest in women less than 25 years old and that it gradually decreased through age 44

years and remained constant through age 64 years. Although Caucasian race is often cited as a risk factor for chronic vulvar pain, most large epidemiologic studies fail to demonstrate differences between Caucasian and African-American women *(10)*. In fact, in one study, Hispanic women were more likely to report chronic vulvar pain when compared with Caucasian women (adj. OR 1.8; 95% CI 1.1–2.7) *(8)*. Women seeking treatment in a vulvar disease clinic are more likely to have had a hysterectomy (adj. OR 3.7; 95%CI 2.3–5.9) than general gynecology clinic controls *(12)*. Age at early intercourse (adj. OR 2.9; 95%CI 1.1–7.6) and use of oral contraceptives for greater than 2 years (adj.OR 1.8; 95%CI 1.1–3.3) are also associated with pain or burning symptoms in young women.

PATHOPHYSIOLOGY

The pathogenesis of chronic vulvar pain is not well understood. Several studies provide support for an altered inflammatory response including decreased natural killer-cell function, impaired response to interferon, less production of interleukin-1-receptor antagonist, and lower production of interferon alpha *(13–15)*. Uncontrolled observational studies show associations between vulvar pain and low back pain/trauma and pelvic surgery *(16–18)*. Most controlled studies fail to demonstrate a role for infectious etiologies such as candidiasis, human papilloma virus, herpes simplex, or excess urinary oxalates *(19–23)*. Additionally, there are no data to support pudendal nerve dysfunction as a cause of vulvar pain *(24)*. Women with vulvodynia appear to have significantly weaker pelvic floor contraction and endurance than asymptomatic controls *(25)*. Although some studies have shown that vulvodynia patients have more depressive symptoms than controls it is difficult to determine cause and effect. Early studies failed to demonstrate associations between sexual or physical abuse *(26,27)*. However, more recent data suggest an association with both physical (OR 4.1; 95%CI 1.7–10) and sexual abuse (OR 6.5; 95%CI 1.2–35) *(28)*.

Embryologic, pathophysiologic, and clinical findings support a common pain pathway in the nervous system. Women with chronic pelvic pain may have heightened nerve sensitivity in the dorsal root ganglia of the spine resulting in visceral hyperalgesia *(29)*. Both chronic vulvar pain and painful bladder syndrome are associated with increased angiogenesis and neural hyperplasia *(30–34)*. Women seeking treatment in a vulvar disease clinic are more likely (adj.OR 2.2; 95%CI 1.2–4.0) to have painful bladder syndrome and more likely (adj. OR 2.1; 95%CI 1.4–3.4) to have a functional bowel disorder than general gynecology controls *(12)*. Twenty percent of women undergoing laparoscopy for chronic pelvic pain are diagnosed with vulvar pain *(35)*. Pain due to spasm of the pelvic floor muscles may also result in dyspareunia. Psychological distress in women with fibromyalgia and irritable bowel syndrome is associated with similar distress seen in vulvodynia *(5)*.

TERMINOLOGY

The terminology used to describe vulvodynia has been in a state of flux for the past 30 years. A consensus among specialty societies such as the International Society for the Study of Vulvovaginal Disease (ISSVD), the American College of Obstetrics and Gynecology (ACOG), and the International Association for the Study of Pain has never been reached. The most recent terminology and classification of vulvar pain by ISSVD defines vulvodynia as "a chronic disorder in women characterized by

provoked or constant vulvar pain of varying intensity without obvious concomitant clinical pathology" *(36)*. Vulvodynia is classified by the site of the pain, whether it is *generalized* or *localized*, and whether it is *provoked, unprovoked*, or *mixed (2)*. The two major types of vulvodynia are generalized and localized. Generalized vulvodynia, previously referred to as vulvodynia, essential vulvodynia, or dysesthetic vulvodynia, specifies involvement of the entire vulva. Localized vulvodynia, previously labeled vestibulodynia or vulvar vestibulitis syndrome, is pain that can be localized to a specific area of the vulva (vestibulodynia, clitorodynia, hemivulvodynia). Patients suffering from provoked vulvodynia have insertional pain with tampons and intercourse and may be apareunic secondary to pain. These patients often cannot wear tight clothing or ride a bicycle. When the vulva is not touched, they may be pain-free. Unprovoked vulvodynia is pain and burning on or around the vulva and vestibule. The area hurts most of the time, even without provocation.

CLINICAL PRESENTATION

Vulvodynia is characterized by unexplained pain or discomfort located anywhere from the mons pubis to the anus. Symptoms leading to the diagnosis of vulvodynia differ among patients; however, painful intercourse is a primary factor leading women with focal, provoked vulvodynia to present for care. Symptoms may be present since childhood, occur after vaginal penetration with intercourse or tampon use, or occur spontaneously after years of painless penetration *(37)*. Vulvodynia may be diffuse or focal, unilateral or bilateral, and constant or sporadic. Patients may describe their pain as severe or mild, and can use descriptors such as burning, stinging, irritating, sharp, prickly, itching, and raw *(38)*. Vulvodynia may also present as urinary urgency, bladder pain, and dysuria. It is not unusual for patients to report symptom-free periods lasting for days or weeks followed by periodic symptom "flares" *(16)*.

EVALUATION

The diagnosis of vulvodynia is made clinically. A thorough history and physical examination are necessary to rule out other etiologies. Diagnoses that should be excluded before a diagnosis of vulvodynia is made include cancer, vulvar intraepithelial neoplasia, vulvar atrophy, lichen sclerosis, lichen planus, chronic vulvovaginal candidiasis, acute infection (herpes simplex virus, trichomonas, and candida), allergic vulvitis, pudendal neuralgia, and vaginismus. History should include detailed pain information including onset and surrounding circumstances, characteristics (location, pain level, radiation) and provoking and relieving factors. It is also important to understand how the patient has been evaluated and treated to date. Psychosocial and sexual histories should be performed including screening for domestic violence and abuse.

Physical examination should be thorough with special emphasis placed on oral, skin, abdominal and genitourinary regions. Visual inspection of the vulva should be performed. Vulvar rashes, fissures, ulcers, or altered mucosa or epithelium are not consistent with vulvodynia and an alternative diagnosis should be entertained. Vulvar erythema may be present but is not specific to vestibulitis and not required for diagnosis *(39)*. Abnormalities noted should be evaluated with a thorough work-up including cultures and possible biopsy. Typical findings include allodynia (pain sensation after innocuous stimulus) and hyperesthesia (out of proportion pain provoked by normally painful stimulus). To test for provoked pain, gently apply a moistened cotton swab to

Fig. 1. A cotton swab is used to test the vestibule for pain to diagnose vulvar vestibulitis. The vestibule is tested at the 2:00, 4:00, 6:00, 8:00, and 10:00 positions. When pain is present, the patient is asked to quantify it as mild, moderate, or severe. (From: Haefner HK. Critique of New Gynecologic Surgical Procedures: Surgery for Vulvar Vestibulitis. *Clin Obstet Gynecol*, Vol 43(3). September 2000, 689–700. with permission.

several areas of the introitus, labia, and hymenal remnants (Figure 1). Enough pressure should be applied to cause a small indentation (3–5 mm). This pressure will illicit pain in almost all women with provoked vulvodynia, and the areas of the posterior vestibule and posterior hymenal remnant are often especially sensitive. The stick of the cotton swab can be broken and the sharp end used to assess hyperesthesia. Provoked vulvodynia (vestibulodynia) is diagnosed by severe pain on vestibular touch or attempted vaginal entry and tenderness to pressure localized within the vulvar vestibule *(40)*. A speculum examination should be performed to evaluate the cervix and vaginal wall epithelium. The examiner should palpate the vagina, cervix, and bladder neck to assess tenderness beyond the vestibule. Vaginismus can be diagnosed by noting involuntary contraction and/or tenderness of the perineal and levator muscles while inserting two fingers into the vagina. Levator muscle tenderness and spasm can also be seen in vulvodynia. A bimanual examination should be performed to evaluate uterine size and adnexal characteristics. Abnormal vaginal secretions should be evaluated by pH and microscopy for active bacterial vaginosis and candidiasis infections. If microscopy is inconclusive, a yeast culture should be performed. Cultures for gonorrhea, chlamydia, herpes, and trichomonas should be considered based on the patients risk profile.

TREATMENTS

The majority of treatment regimens for vulvodynia have not been rigorously studied. Data consist primarily of retrospective studies or case series. The goals of medical treatment of vulvodynia are to reduce the level of pain and degree of bother so as to improve quality of life. Treatment goals should be individualized for each patient. Treatments including behavioral, medical (oral, topical, and injection), physical, and surgical therapies are presented in Table 1.

Table 1
Treatments Including Behavioral, Medical (oral, topical, and injection), Physical, and Surgical Therapies

Treatment	*Dosing*	*Side effects*	*Precautions*	*Level of evidence**
Amitriptyline (Elavil®, Tryptanol®, Endep®, Elatrol®, Tryptizol®) Nortriptyline (Aventyl®, Pamelor®)	10 or 25 mg nightly, increase weekly, do not exceed 100–150 mg	Sedation, dry mouth, constipation	Do not stop abruptly, use lower doses in elderly	II *(45)* III *(44, 46–48)* IV *(44)*
Gabapentin (Neurontin®)	300 mg daily × 3 days, increasing dose Q3 days to reach 300 mg TID, increase up to 3600 mg/day	Headaches, dizziness, nausea, vomiting, ataxia, fatigue, visual disturbances	Do not exceed 2700 mg/day in the elderly	II *(50)* IV *(51)*
Capsaicin (Capsagel®, Salonpas-Hot®, Zostrix®)	0.025%–0.05% cream applied to vulva QD–QID	Severe burning on administration	May use lidocaine cream or oral narcotics, pain will return upon discontinuation	II *(53,58)* IV *(57)*
Lidocaine (topical) (Xylocaine®, Xylocard®)	5% ointment applied nightly or PRN to vestibule	Erythema	Do not exceed 20 g of ointment in 24 h	II *(54)*
Botulinum toxin A (Botox®, Dysport®)	20–50U injected into the vestibule, perineal body, or levator ani	None reported	Ensure proper injection placement No data available on repeat dosing	I *(67)* II *(68–70)* IV *(88)*

Physical therapy/ Biofeedback	Evaluation and treatment by qualified physical therapist, usual treatment regimen: 7–10 sessions followed by home exercises	None reported	Patient must be committed to continuing exercises	I *(80)* II *(77,79)*
Surgery	Vestibulectomy	Infection, bleeding, scaring, worsening pain	Consider after all other treatments have failed, only use for localized, provoked pain	I *(80)* III *(86,87)*

* from Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)

QD = daily, BID = twice daily, TID = three times daily, QID = four times daily, PRN = as needed

Vulvar Care Measures

Patients with vulvodynia often try multiple vulvar treatments and have excessive hygiene practices. Gentle care is recommended, and patients who have used multiple treatments may experience improvement after cessation of all treatments. Initial suggestions include avoiding irritants such as perfumes, detergents, soaps, shampoos, and dyed toilet paper. The vulva is to be washed gently with water or a mild hypoallergenic soap and patted dry. Rinsing and patting the vulva dry after urination may be helpful. An emollient without preservatives such as vegetable oil or plain petroleum jelly may be used to provide a barrier for the vulva and improve tissue moisture. Cotton underwear should be used during the day and wearing no underwear while sleeping may be helpful. Adequate lubrication during intercourse is recommended. Ice packs or cool gel packs may be useful in moderation for symptom relief *(41)*.

Dietary Changes and Dietary Supplements

One proposed cause of vulvodynia is hyperoxaluria and microscopic oxalcrystalluria. This hypothesis emerged after a woman with refractory vulvar vestibulitis was noted to have periodic hyperoxaluria and was successfully treated with a low oxalate diet and calcium citrate *(42)*. This has led clinicians to recommend calcium citrate and a diet low in oxalate to inhibit urinary calcium oxalate crystal formation. A low oxalate diet prohibits rhubarb, peanuts, spinach, celery, chocolate, tea, tofu, pecans, raspberries, and other foods. The daily recommended doses of calcium and citrate are 1200 mg and 5700 mg, respectively, in six divided doses. It is important to prescribe calcium citrate without vitamin D to prevent excess dosing of the fat-soluble vitamin. Prospective trials assessing this intervention have provided mixed results. Twenty-four hour urinary oxalate measurements were found to be similar in vulvar pain patients and pain-free volunteers *(22)*. Vulvar pain patients diagnosed with hyperoxaluria and subsequently treated with low-oxalate diets and calcium citrate had disappointing results, with 24% noting improvement, but only 10–14% able to have pain-free intercourse *(22,43)*. Based on these data, a low oxalate diet does not appear to be effective for most women with vulvodynia, but it is reasonable to offer this early in the treatment course because of its low risk and cost.

Oral Medications

Tricyclic Antidepressants

The use of tricyclic antidepressants in women with vulvodynia is largely based on successful treatment of neuropathic or burning pain in patients with glossodynia (burning tongue), post-herpetic neuralgia, and other cutaneous dysesthesias. Although amitriptyline is usually the first line tricyclic antidepressant for vulvodynia, successful use of nortriptyline has been reported *(44)*. Amitriptyline or nortriptyline may be started at 10 mg nightly and increased weekly by 10 mg, using the lowest dose that is clinically effective. Common side effects include dry mouth, drowsiness, dizziness, constipation, and weight gain. There are no randomized placebo-controlled trials using antidepressants to treat chronic vulvar pain. A large uncontrolled trial treated 168 patients with vulvar vestibulitis with up to 75 mg of amitriptyline daily and noted a 60% response rate *(45)*. Several smaller studies reported similar response rates ranging from 47–56% *(46,47)*. Patients most likely to respond to amitriptyline are women aged

43–85 years old, with constant or unremitting discomfort, and those with additional urethral, rectal, and/or back pain *(48)*.

Anticonvulsants

Gabapentin is an anticonvulsant that also has proven effectiveness in the treatment of neuropathic pain *(49)*. Gabapentin can be started at 300 mg daily for 3 days and then increased to 300 mg twice daily for 3 days followed by 300 mg 3 times daily. It can be increased to a total of 3600 mg per day, ideally divided into three separate doses. Common side effects include somnolence, dizziness, ataxia, and fatigue. Support for the use of gabapentin in patients with vulvodynia consists of small uncontrolled case series. Partial or complete relief was seen in 82% of patients treated with 1200 mg of gabapentin *(50,51)*. Relief was noted between 2 and 4 weeks of treatment with no late treatment failures. Similarly, in retrospective studies, patients who were treated with anticonvulsants rated its effectiveness as 3.2 of 5 and 80% elected to continue the medication *(47)*. Although gabapentin is the most commonly used anti-convulsant for vulvodynia, other anti-convulsants such as carbemazepine and topiramate have been used despite limited data supporting their use. In one study, carbemazepine was noted to be of little benefit, with a 13% response rate in 30 patients with vulvodynia *(45)*.

Other Oral Medications

Several researchers have implicated vulvovaginal candidiasis as a potential cause of vulvodynia because some women with vulvar vestibulitis first noted symptoms following a yeast infection. However, data from a randomized controlled trial established that vulvodynia patients should not be treated empirically with oral fluconazole *(52)*. A sample of 40 patients with vulvar vestibulitis were treated with a low oxalate diet and calcium citrate for 6 months and half of these women were randomized to 150 mg of oral fluconazole weekly for 6 months. There were no subjective differences noted between treatment and control groups 3 months after treatment completion. Other medications including isoretinoin, dapsone, and acyclovir have been studied in small series. Due to poor tolerability or minimal improvement, these medications are not currently recommended treatments for chronic vulvar pain *(53)*.

Topical Medications

Because many patients with chronic vulvar pain have localized symptoms and currently available oral medications have substantial central nervous system side effects, topical medications have become popular. Topical local anesthetics are commonly recommended for patients for transient relief of vulvar pain and dyspareunia based on clinical experience and a few studies *(47,54)*. Nightly use of 5% lidocaine in a cotton ball by women with vulvar vestibulitis led to significant improvement in post-treatment VAS-pain scores, intercourse-related pain scores, and a higher proportion of women able to have intercourse (pretreatment 36% vs. post-treatment 76%; $p = .002$) *(54)*. Local anesthetics can also be used on an as-needed basis and in conjunction with other treatments. Five percent lidocaine gel is sometimes irritating, necessitating the use of 2% gel. Care in dosing is necessary to prevent inadvertent overdose.

Topical steroids have been investigated as treatments for vulvodynia based on histologic findings of inflammation. One randomized, double-blind, crossover trial demonstrated that clobetasol 0.05% ointment significantly reduced pain, tenderness,

and erythema compared with hydrocortisone 0.5% ointment in patients with vulvar vestibulitis *(55)*. No other data support the use of topical steroids in patients with vulvodynia.

Topical capsaicin has been used for a variety of neuropathic pain conditions. Capsaicin acts as an agonist of specific vanilloid receptors located on the sensitive peripheral terminals of nociceptors and activates A-delta sensory neurons and unmyelinated C fibers. The initial application of capsaicin causes significant burning but later results in a long-lasting desensitization to burning and pain *(56)*. Data on the effectiveness of capsaicin are mixed. Several authors have demonstrated that capsaicin cream 0.025–0.05% may have short-term benefits when applied to the vulva 4–5 times daily for at least 4 weeks and tapered over several months *(53,57)*. The patient must be motivated and committed to continuing treatment once improvement is noted because symptoms may return after cessation of treatment *(58)*.

Cromolyn cream has been suggested as a treatment for vulvodynia based on data demonstrating increased numbers of mast cells in tissue samples of patients undergoing vestibulectomy *(59)*. However, cromolyn is no longer recommended after a double-blind placebo-controlled trial evaluating 4% cromolyn cream for 3 months for the treatment of vulvar vestibulitis failed to show improvement compared with placebo (54% vs. 38%; $p = \text{NS}$) *(60)*.

Data on hormonal treatment such as topical estrogen and progesterone cream for vulvodynia are limited to small pilot studies showing no response *(47,53)*. However, vaginal estrogen could be given in women with vulvodynia who have concurrent vulvovaginal atrophy. A single study noted some improvement in pain with intercourse using 0.2% nitroglycerine cream at least three times per week and before sexual relations. Unfortunately, 65% of patients experienced headache *(61)*.

Injection Therapy

Based on studies demonstrating moderate inflammation in the epithelial stroma with lymphocytes, plasma cells, and histiocytes resulting in a chronic inflammatory reaction, investigators have postulated that anti-inflammatory drugs may be useful *(19,62)*. Clinical data are limited to a small retrospective study. Patients with vulvar vestibulitis underwent methylprednisone and lidocaine injections of the vulvar vestibule weekly for 3 weeks, with 68% responding favorably, including 32% noting complete resolution of symptoms with no relapse reported at 9 months. Five patients available for 24-month follow-up reported no need for further treatment *(63)*.

Botulinum toxin A may be useful in patients with vulvodynia who have skeletal muscle hypertonicity as with vaginismus. Botulinum toxin A is known to have a temporary paralytic effect on the surrounding skeletal muscles *(64,65)* and may alter innervation and/or sensitization of thermoreceptors and nociceptors in the vestibular mucosa *(66)*. Injection of 80 units of botulinum toxin A into the pelvic floor muscles of women with chronic pelvic pain and pelvic floor spasm reduced the rate of dyspareunia and pelvic floor pressure when compared with placebo *(67)*. In an open-label, pilot study, patients with provoked vestibulodynia had significantly decreased pain scores for up to 14 weeks after botulinum toxin injections of the vestibular epithelium *(68)*. Botulinum toxin injections of the levator ani, vestibule, and perineal body in patients with vulvodynia were also effective in decreasing subjective pain scores *(69)*. However, results from small case series in women with vulvodynia are conflicting, and injection

techniques and botulinum toxin dosing are not currently standardized *(70)*. Nevertheless, the available data indicate that botulinum toxin injections of the vestibule and levator ani are well-tolerated and safe and may be effective in select patients.

The human papilloma virus (HPV) has been implicated as a potential etiology of vulvodynia and decreased interferon production has been noted in some vulvodynia patients *(70,71)*. These findings have led clinicians to treat HPV-associated vulvodynia with interferon. Intralesional alpha interferon has been reported to successfully treat HPV-associated vulvodynia in 70% of patients, whereas subcutaneous delivery only has a 16% success rate *(72)*. Intramuscular injections of beta interferon have also been shown to be effective in small, uncontrolled trials *(73)*, whereas intramuscular alpha interferon was showed to be cost-effective in patients with vulvar vestibulitis associated with human papilloma virus *(74)*. Although these data support the use of interferon, issues such as dose, route of administration, indications, and side effects need to be clarified before recommending its use.

Physical Therapy

It is not uncommon for patients with vulvodynia to have dysfunction of the pelvic floor muscles. Localized tissue disturbance may result in myofascial hyperirritability *(75)*. Furthermore, the principal motor and sensory nerve fibers to both the vulva and the pubococcygeous are branches of the pudendal nerve plexus containing fibers from S3 to S4. Women suffering from vulvar vestibulitis have significantly more vaginal hypertonicity, lack of vaginal muscle strength, and restriction of the vaginal orifice than women without vulvar pain *(64)*. As a result, pelvic floor physical therapy is increasingly included in treatment regimens for vulvodynia and may be effective in relieving dyspareunia and improving sexual function in women with vulvar vestibulitis. Physical therapy for an average of seven sessions led to complete or great improvement in 52% of women with vulvar vestibulitis, including 9% reporting complete relief, whereas 89% said they would undergo physical therapy again. Patients also reported decreased pain during intercourse and increased levels of desire and arousal *(76)*. Patients with vulvar vestibulitis who completed home exercises with EMG biofeedback for 3 months followed by home exercises without EMG for 6 months were noted to have significantly increased pelvic floor muscle contractions and significantly decreased resting tension levels and muscle instability. Subjective reports of pain decreased 83%, with 78% of patients resuming intercourse, and 52% of patients reporting pain-free intercourse after treatment *(77)*. Long-term outcomes in generalized vulvodynia patients treated with surface electromyography (sEMG)-assisted pelvic floor muscle rehabilitation are also encouraging. Of patients who were symptom-free at the end of their therapy sessions, 88% reported experiencing no vulvar pain since completion of the treatment and all the patients with a partner reported regular sexual intercourse without pain *(78)*. Prospective analysis of the use of sEMG in vulvar vestibulitis patients revealed 52% of treated patients reporting markedly diminished introital tenderness and 93% of patients able to resume sexual function without discomfort *(79)*. However, in a randomized, controlled trial in which several treatment modalities were compared in patients with vulvar vestibulitis, only 35% of patients treated with sEMG reported great improvement or complete relief of pain *(80)*.

Other Treatment Modalities

Acupuncture has been reported to have success rates of 42% in patients with vulvodynia and 85% in patients with vulvar vestibulitis. Although these trials were uncontrolled and used different techniques, the treatments were well tolerated *(81,82)*. Spinal cord neuromodulation has also been reported for intractable generalized vulvar pain with some success *(83,84)*.

Surgery

Women with localized vulvodynia (vulvar vestibulitis) who have pain and tenderness on the vulvar vestibule especially over both Bartholin glands, who have failed all medical and conservative treatments, are candidates for surgical intervention. Surgical treatment should only be considered after all non-surgical treatment measures have not provided adequate relief. The surgical treatment that appears from cohort studies to be the most efficacious is partial vulvar vestibulectomy with advancement of a vaginal flap to cover the area. In the past, surgeons have attempted laser vaporization of portions of the vulvar vestibule, but these surgeries are no longer done because of high complications and poor outcomes. Variations of the partial vulvar vestibulectomy technique involve the amount of vulvar skin removed, the depth of the dissection, and whether the two Bartholin glands are simultaneously removed with the vulvar skin. These variations and the radicality of the vestibulectomy procedure have not been compared in any randomized surgical trials. Herein, we describe a commonly performed technique.

Before surgery is done for vulvar vestibulitis, patients should be carefully counseled about the surgical procedure, its risks and benefits, and a realistic description of the likely surgical results including the chance of complete cure, partial cure, and failure or worsening after surgery. For patients with levator muscle spasm or vaginismus, pre- and post-operative consultation with a physical therapist is useful and recommended.

The surgical technique is done under general or regional anesthesia. After the patient is placed in lithotomy position with her legs elevated and abducted, the vulva, vagina, and perineum are sterily prepped and draped for surgery. The U-shaped crescent of tissue that includes the inner vulvar vestibule to the hymen and including both Bartholin gland openings is outlined with a sterile marking pen. The area is infiltrated under the epithelium with a vasoconstricting solution such as 0.5% lidocaine and epinephrine 1:200,000. Deeper injection with Marcaine also can be done to help with post-operative pain relief.

The skin is incised at the previously marked area, and the vulvar vestibule tissue is undermined sharply with Metzenbaum scissors. Occasionally, a small Bartholin gland cyst or nodularity is palpable, and this should be removed during the surgical procedure. As previously noted, it is controversial whether both Bartholin glands should be removed at this time and expert opinion varies. The vulvar skin is dissected under the level of the hymen and then into the rectovaginal septum for approximately three additional centimeters. This allows for mobilization of the posterior vaginal wall and epithelium, over the excised vulvar vestibule. After the vulvar skin is completely freed from the underlying tissue, the crescent of vulvar vestibule including the hymen and any Bartholin gland tissue is removed and sent to Pathology. Strict hemostasis is necessary before skin closure to avoid post-operative bleeding or vulvar hematomas. The vaginal skin flap is undermined and advanced until it reaches the outer vulvar incision. A deep layer of fine absorbable sutures is placed for hemostasis to close

the space and to stabilize the advanced vaginal flap. The skin is then closed with interrupted fine absorbable suture.

The surgical procedure may be limited or extensive depending on the patient's symptoms. Specific tender areas such as distortion and/or pain from an episiotomy scar can require a more extensive dissection of the perineum or excision as needed. Both extensive and limited types of surgery have been shown to relieve painful intercourse associated with vulvar vestibulitis.

Vulvar vestibulectomy is typically performed as an outpatient surgery. Icepacks are used to relieve immediate discomfort and sitz baths can be used as needed post-operatively. Oral narcotics and non-steroidal anti-inflammatory medications are prescribed for pain relief. The patient is generally seen after 2–4 weeks to examine the vulvar incision and to discuss the need for further pain management, relaxation techniques, physical therapy, and possibly small vaginal dilators to help keep the scar from contracting. Healing of the surgical site typically takes 4–6 weeks with some surgical tenderness lasting longer. Post-menopausal women are routinely given estrogen vaginal cream to help treat vulvovaginal atrophy and to promote healing.

Complications following the surgery are uncommon and include post-operative bleeding, skin infection, hematoma, and partial or complete wound separation. More delayed adverse outcomes include Bartholin gland cyst formation, vaginismus, diffuse burning, and vaginal stenosis.

Most studies report significant improvement or complete resolution of pain in 70–90% of patients *(85,86)*. Schneider et al. reported that 83% of patients were satisfied with the results and would recommend the surgery to other women with this clinical problem *(87)*. In a small percentage of cases, the pain may persist or even worsen after surgical treatment. Two pre-operative factors associated with unfavorable surgical outcome are constant diffuse vulvar burning or pain and pain associated with the first episode of sexual intercourse *(86)*.

In one of the few randomized comparisons of surgery versus behavioral therapy and biofeedback, vulvar vestibulectomy was shown to be significantly more successful than surface EMG biofeedback *(80)*. This study showed that behavioral therapy and biofeedback improved measures of psychological adjustment and sexual function, although patients who underwent surgery had significantly better reductions in pain measures after treatment. This result, however, must be tempered with the finding that 24% of women randomized to vestibulectomy withdrew from the study before undergoing the surgical procedure and 9.1% of patients who underwent vestibulectomy reported being worse post-treatment compared with pre-treatment *(80)*.

CONCLUSION

Vulvodynia, a chronic pain condition of the vulva, significantly affects the quality of women's lives. Its cause is currently unknown, but basic science studies reveal that there are potentially many different etiologies. There are limited Level I data supporting specific treatments for vulvodynia, but uncontrolled studies have examined the use of oral, topical, and injection medical therapy, as well as physical therapy. Given the current lack of data, it is vital to discuss the patient's treatment goals before beginning therapy and make appropriate treatment plans. Outcomes for surgery to treat vulvar vestibulitis are favorable, but this treatment option should be used only after all others are exhausted.

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18 Evaluation and Management of Disorders of the Female Urethra

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SUMMARY

Historically, urethral syndrome has been defined as symptoms suggestive of a lower urinary tract infection in the absence of significant bacteruria with a conventional pathogen. In the modern era, components of this term have been separated out into new disease entities such as overactive bladder, functional bladder outlet obstruction, and pelvic pain syndrome including dyspareunia and vulvodynia. Proper treatment is best initiated by correct usage of the terminology that describes the patient's symptoms and evaluation, followed by symptom-focused treatment.

KEY WORDS: Urethra; urethral syndrome; lower urinary tract; overactive bladder; functional bladder outlet obstruction; pelvic pain syndrome; dyspareunia; vulvodynia.

CONTENTS

INTRODUCTION

The term "urethral syndrome" encompasses a myriad of female pelvic health issues that span the disciplines of Psychology, Immunology, Infectious Disease, and Urology. An inordinate number of descriptions have been used to describe this disease, such as

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female aseptic dysuria, female prostatitis, and abacterial cystititis. This lack of proper nomenclature has made it difficult for clinicians to speak scientifically on the subject matter. Subsequently, evidence-based material on this subject matter is also lacking. In the modern era, however, it is not uncommon for urologist, gynecologist, and pelvic health specialist to evaluate patients with a history of this diagnosis. Although the term "urethral syndrome" appears to be anachronistic, it remains the diagnosis of choice for many clinicians because of a lack of objective finding in this patient population. The aim of this manuscript therefore is to educate the clinician on the current body of knowledge regarding this syndrome in order to assist in the proper evaluation and treatment of these patients.

Urethral syndrome is defined as symptoms suggestive of a lower urinary tract urinary infection but in the absence of significant bacteruria with a conventional pathogen *(1)*. Symptoms may include burning with urination, frequency and urgency, pain or discomfort localized to the urinary meatus. Non-infective causes that may be involved in this syndrome include inflammatory disorders, allergic, traumatic, and anatomical disorder such as diverticula and post surgical scarring. The constellation of the aforementioned symptoms often lead patients to seek treatment for presumed urinary tract infection, although cultures typically do not show any conventional bacterial growth and pyuria (more than 5 WBC per HPF) is normally absent. Patients with complaints of urethral syndrome may also have dyspareunia and worsening of symptoms related to sexual intercourse.

Although symptoms of frequency, urgency, and pelvic pain have been used to describe the patient with urethral syndrome *(2)*, there appears to be much overlap with the overactive bladder (OAB) and interstitial cystitis patient. Discernment between these two groups has made the diagnosis of urethral syndrome very difficult. The clinical burden to make the proper diagnosis will therefore always be paramount prior to implementation of the therapy.

EPIDEMIOLOGY

True epidiomological studies on the incidence and prevalence of urethral syndrome are lacking. Medline search does however reveal small single institution studies in the literature. In a Turkish study, urethral syndrome defined as urinary irritation with dysuria, urgency, and pollakuia was identifed in 35 women from cohort on 235 premenopausal women from a gynecological clinic. Univariate and multivariate analyses identified grandmultiparity and delivery without episiotomy as risk factors, for urethral syndrome *(3)*. The lack of other risk factor identification is most likely because of the lack of a consistant identifiable population.

ETIOLOGY

Disorders of the urethra are often multifactorial in nature. Psychological, neurological, infectious, and inflammatory disorders may all be identified as root causes of urethral syndrome resulting in voiding dysfunction. Urethritis has been associated in patients with rheumatological syndromes such as ankylosing spondylitis. Fifteen of 32 patients with urethral syndrome were found to be HLA-B27 positive in one study, indicating that at least some symptoms of urethral syndrome may be autoimmune in nature *(4)*. Infectious etiologies may include an exposure to Chlamydia. One

observational study identified that up to 19% of female partners of men with non-gonoccocal non-clamydial urethritis may be infected with Chlamydia. It is unclear whether these women presented with urethrtitis at the time of their identification or may go on to develop urethral syndrome symptomatology *(5)*. This relationship between unrecognized urethral infection and urethral syndrome in women remains unclear. Parsons describes urethral syndrome as an early stage of lower urinary tract epithelial dysfunction. Lower urinary tract epithelial dysfunction is briefly described as a permeability of the bladder epithelium to toxins such as potassium. In his study, 64 of 116 (55%) women with a diagnosis of urethral syndrome were found to have positive findings on potassium sensitivity testing *(6)*.

DIAGNOSIS

No specific diagnostic criteria are available for urethral syndrome. Rather, it appears to be a diagnosis of exclusion based on patient symptamotology. A detailed voiding history should be obtained with emphasis on recent changes in voiding patterns. Queries should also include sexual history, abuse history, and occurrence of pelvic trauma. Physical examination therefore is designed to rule out other treatable causes of lower urinary tract symptoms. General examination of the female patient requires a basic understanding of urology, gynecology, and neurology. General examination should be comprehensive and encompass any medical co-morbidities that have been revealed in the history. The abdomen should be inspected for scars as indications of pelvic surgery. During the pelvic exam, observation of rashes vulva and labia may indicate local yeast infection or irritation from fecal or urinary incontinence. With the aid of a lighted speculum, the vaginal mucosa should be inspected for signs of atrophy, discharge, or blood. Age appropriate cancer screening should be obtained in all patients. Cough or Valsalva maneuvers in the supine position may elicit stress incontinence; however, a standing position may be needed to demonstrate uterine descensus and associated incontinence. A neurological evaluation of the lumbar and sacral nerve distribution should be performed during the initial exam. Inspection of the lower back may reveal occult lumbar injuries. Assessment of the bulbar cavernosal and clitoral reflexes may reveal dysfunction of the afferent and efferent pathways of the sacral nerves. Bimanual examination with palpation of the levator ani muscle may reveal levator spasm. Fullness of the anterior vagina or urethra may indicate the presence urethral diverticula. Any suspicion of this etiology is best investigated with a pelvic MRI *(7)*. Rectal examination may reveal constipation, which may exacerbate urinary conditions and worsen with antimuscarinic therapy *(8,9)*. In addition to examination, vaginal or urethral cultures for mycoplasma and ureaplasma may indicate occult bacterial infection of the urethra which can often lead to lower urinary tract symptoms *(10)*.

Following physical examination, cystoscopy can be performed if there is any suspicion of bladder outlet obstruction, evidence of microscopic hematuria, or anatomic abnormality. For patients with lack of pain as a portion of their symptoms, urodynamics may provide addition information such as bladder capacity, evidence of detrusor overactivity, or pain with filling of the bladder.

Therapeutic Options

Treatment of urethral syndrome is generally directed toward the specific etiologies identified during physical examination. Because of the generality of symptoms that

are covered by this terminology, several treatment options may apply with varying amounts of success.

For patients with "urethral syndrome" and a predominance of the vulvar tenderness on exam with the lack of any other objective findings, topical anesthetics may be useful. Xylocaine® jelly (2%) or 5% lidocaine ointment applied liberally to the introitus may provide several hours of relief and can be used before sexual activity if a history of dyspareunia has been illicited. Other agents such as estrogen, capsaicin, and cool compresses may also be of therapeutic benefit. No randomized trials are available at this time. For patients with more severe discomfort, usage of neuropathic medications such as tricyclic antidepressants and gabapentin may be indicated. Many patients may perceive the prescription of antidepressants as a lack of validation of their symptoms and refrain from taking the medication. Therefore, it is important to counsel patients on the usage of these medications in the treatment for neuropathic pain *(11)*. Pain management services may also be sought out to provide other treatment modalities such as acupuncture and pudendal nerve blocks for the refractory patient.

Antibiotic therapy for urethral syndrome is appropriate within the diagnosis of an infectious urethritis. Positive urethral cultures for mycoplasma and ureaplasma urealyticum should be treated appropriately. At the author's institution, initial therapy with a 2-week course of doxycycline 100 mg two times a day utilized. Treatment of sexual partners with the same regimen is performed to reduce the risk of the risk of recolonization. Refractory cases may additionally be treated with Azithromycin 1 g. Other antibiotics such as flouroquinilones have shown very good in vitro activity against both mycoplamsa and ureaplasma species *(12)*.

Pelvic floor physical therapy may also be of great utility in patients without identifiable infection or pain complaints. Symptoms localized as urinary urgency and frequency with or without pelvic pain may be greatly improved with techniques to relax myofascial trigger points. In a study of 42 women with symptomatic urinary urgency and frequency, moderate to marked improvement was achieved in 83% with a treatment regimen of lateral and posterior stretching/compression maneuvers of the urethrovaginal sphincter and pubovaginalis muscles *(13)*. Other studies have identified the usage of biofeedback, bladder training, and external sphincter relaxation as effective treatment option for patients who are refractory to initial antibiotic therapy *(2)*.

The usage of urethral dilation for the treatment of urethral syndrome has been practiced by many urologists. In a survey of urologists who trained more than 10 years ago compared with urologists more recently trained, the latter group identified no efficacy in urethral dilation *(14)*. Outside of the treatment of urethral stenosis that is congenitally acquired or because of surgery, this practice appears to have no evidence-based role in the modern era.

Neuromodulation in the form of Botulinum Type A Toxin or the InterStim® device appears to have a limited role in the treatment of urethral syndrome. For patients with a predominance of irritative or obstruction symptoms, sacral neuromodulation seems to provide substantial resolution of symptoms. In a multicenter study on the treatment of urgency and frequency symptoms, sacral neuromodulation was found to provide a significant improvement in terms of voids per day, volume per void, and degree of urgency *(15)*. Botulinum toxin has been found to be efficacious in patients with outlet obstruction or failure to relax the sphincter. In a study of males and females with voiding dysfunction, low dosages of 50–100 u of Botulinum toxin was found to provide an 85% relief of obstruction-voiding patterns with resolution of intermittent

catheterization and need for chronic catheter usage *(16)*. A lack of evidence supports the usage of these two modalities in patients with pain as the major urethral syndrome component.

Surgical treatment options for urethral syndrome would be directed at identifiable anatomic disorders such as urethral stenosis or urethral diverticulum. It is beyond the scope to this article to discuss these surgical interventions.

CONCLUSION

In the modern era, the term "urethral syndrome" is best left as a historical terminology that describes a constellation of symptoms that exist without an identifiable cause. The components of this term have been separated out into new disease entities such as pelvic pain syndrome including dyspareunia and vulvodynia, overactive bladder (urgency and frequency), and functional bladder outlet obstruction. With the standardization of urinary terminology, these subsequent new terms share minimal overlap and are designed to allow intellectual discussion between researchers *(17)*. In short, the failure of the term urethral syndrome to adequately communicate a disease process has led to its replacement with the aforementioned individual terms. The proper treatment of a suspected urethral syndrome patient would therefore be best initiated by the correct usage of the terminology that best describes these patients' symptoms followed by a symptom-focused treatment. The continued lack of evidence-based material utilizing this term affirms its abandonment by the scientific community. Therefore, it is hopeful that this manuscript has provided clarification and closure for a poorly described medical syndrome.

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19 Psychosocial Considerations in Female Genitourinary Pain

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SUMMARY

This chapter explores female genitourinary (GU) pain from a psychological perspective, including the question of whether it is a psychosomatic or somatoform disorder. Dyspareunia and vaginismus are explained in the context of the DSM-IV-TR classification as psychiatric sexual dysfunctions. A newer paradigm is explored, viewing female GU pain, or the vulvodynias, as chronic pain disorders as opposed to sexual dysfunctions. Subtypes of vulvodynia, both organic and non-organic (or idiopathic) in etiology, are presented. Psychosocial factors in the idiopathic female GU pain disorders, known as dysesthetic vulvodynia (DV) and vulvar vestibulitis syndrome (VVS), are explored. Psychosocial strategies recommended for use in the multidisciplinary treatment of female GU pain and suggestions for future research are reviewed.

KEY WORDS: dyspareunia; vulvodynia: idiopathic, dysesthetic, generalized, essential; female genitourinary pain; localized dysesthesia; psychological treatment; psychosocial factors; psychosomatic; chronic vulvar pain; sexual pain disorders; sex therapy; multidisciplinary treatment; psychiatric sexual dysfunctions; chronic pain disorders, idiopathic pain; vestibulodynia; vulvar vestibulitis syndrome.

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FEMALE GU PAIN: PSYCHOSOMATIC OR NOT?

Vulvar pain, regardless of its etiology, is a distressing problem for many women. Although its prevalence is unknown, vulvodynia is estimated to affect at least 200,000 women in the US today *(1)*; moreover, based on a lifetime cumulative index of 16%, it is expected to affect as many as 14 million American women during their lifetime *(2,3)*. There are many documented organic causes of vulvar pain, including inflammatory, neurologic, dystrophic, traumatic, hormonal, anatomical, sexual, infectious, allergic, chemical, urological, proctological, rheumatological, and muscular problems; however, in many cases of female GU pain, an organic basis cannot be found *(4)*.

It appears that vulvodynia may be a women's health concern of a greater magnitude than previously believed, because unexplained, or idiopathic, vulvar pain lasting 3 months or longer was reported by 16–18% of the female population *(2,5)*. Despite its relatively high prevalence, many physicians adhere to the outdated belief that vulvodynia is purely psychosomatic in origin. This practice results in misattribution of the vulvodynia sufferer's pain and often causes a delay in appropriate treatment; interestingly, both these factors have been found to increase the patient's experience of pain and emotional distress *(6,7)*. It is imperative, therefore, to increase physician and patient awareness of this condition to allow its sufferers to be properly diagnosed and treated in a timely fashion and without being dismissed as somatizers. It is this unexplained, or idiopathic, vulvar pain that will be the primary focus of this chapter.

Coital or vaginal pain without evidence of organic basis historically was viewed as a psychosomatic manifestation of women's unresolved emotional problems. These included problems with psychosexual conflict, sexual trauma, relationship difficulties, or psychiatric issues such as guilt, dependency, anxiety, depression, somatoform, and personality disorders. *(8–12)*. Dodson and Friedrich *(9)* named this condition *psychosomatic vulvovaginitis* and emphasized the emotional lability and unwillingness of patients with this condition to accept a psychophysiologic cause for this problem. Woodward *(12)* reported four major categories of psychopathology and environmental influences on psychosomatic vulvovaginitis, including parental attitudes toward sex, resentment toward sexual partner, anxiety or nervousness, and reactions to life stressors.

Huffman *(10)* suggested that psychogenic dyspareunia is caused by cerebral factors that lead to sexual avoidance behaviors. Such factors include fear of pain at first coitus, aversion to sex because of misinformation, fear of "unclean" acts, memories of previous sexual abuse or painful coitus, fear of pregnancy, ambivalence or refusal to "submit" to a "dominant" male partner during intercourse, or aversion to a partner's appearance or sexual behaviors. Noting the bias of a "dominance of heteronormativity" evident in a traditional understanding of sexuality, Kaler *(13)* soundly criticized these psychoanalytically based explanations for female sexual pain conditions.

Although there is often a significant psychological component to vulvar pain disorders *(14–18)*, there is little conclusive evidence to support the notion that women experiencing vaginal pain disorders typically suffer from a greater incidence of premorbid mental disorders, relationship problems, or sexual abuse histories than those without vulvodynia *(8,19–23)*. Wylie et al. *(24)* suggested that the best approach to understanding the psychological aspects of vulvodynia may be to consider them contributory and associative, rather than causative, and to evaluate their effects on vulvodynia patients' illness behaviors, sexual relationships, and interpersonal relationships with clinicians.

Purely psychosomatic sexual pain disorders such as psychogenic dyspareunia may exist, but they are likely the exception to the rule *(10,12,25)*. Although female genitourinary (GU) pain conditions often have no obvious or identifiable physiological or organic etiology, they are now hypothesized to be the result of prior viral or bacterial infection, irritation, allergic response, immune system dysfunction, genetic predisposition, traumatic injury, or central sensitization of the nervous system *(5,24,26,27)*. Although these biological factors may be exacerbated by stress *(5)*, the pain itself is not attributed solely to an underlying psychological disturbance.

The lack of objective physical findings can be especially frustrating for vaginal pain sufferers longing to find the underlying cause for their pain condition so that they may resume a once satisfactory sexual relationship. This is especially true when these women are told that their condition is a psychological one simply because of the lack of physical findings, and often without any supporting evidence of psychiatric disorder or relationship disturbance. Understandably, emotional distress and psychiatric disorders such as depression often develop as a result of the intense, unremitting symptoms of an unexplained sexual pain condition *(8,28)* and potentially lead to disturbance in both the patient and in the relationship with her sexual partner.

In addition, women's cognitive attributions for the cause of their pain affect the intensity of their pain experience. Meana et al. *(6)* found that women who believed the cause of their coital pain to be psychological in origin experienced a greater amount of pain and emotional distress than women whose attribution for their pain was physiological in nature. Along these lines, Graziottin and Brotto *(25)* issued an imperative for physicians to abstain from telling vulvodynia patients that the pain is "all in your head." These authors emphasized the importance of treatment providers' efforts to build a therapeutic alliance with the patient based on a respectful understanding of the emotional needs inherent to her experience of a painful sexual condition. Granot and Levee *(29)* further examined the role of attribution in vulvodynia patients' pain experience. These authors found that multiple psychosocial factors influenced VVS patients' perception of pain, including fear or anticipation of pain, somatization tendencies, poor body image, and catastrophizing thought patterns. Granot and Lavee also emphasized the role of cognitive appraisal in catastrophization, in that it may be responsible for enhanced pain perception (i.e., through rumination and increased attention to painful stimuli) and emotional distress in VVS patients *(29)*.

Since the 1980s, the understanding of female GU pain with no identifiable causative agent has evolved from purely psychosomatic explanations *(8–10, 12)* to a combination of physiologic and psychological explanations *(1,14,30)*. Binik et al. asserted that all cases of dyspareunia contain both psychological and organic components and recommended that each be addressed to ensure comprehensive treatment *(14,30)*. A potential outcome of this paradigm shift to a more holistic understanding of idiopathic vulvar pain may be that some of the emotional stigma and resultant suffering of women

with GU pain will be alleviated as more providers of care adopt a comprehensive, compassionate understanding of patients' mind–body experience.

FEMALE GU PAIN AS PSYCHIATRIC SEXUAL DYSFUNCTIONS

The relevant literature contains a multitude of conflicting or overlapping definitions of vulvar pain disorders, which adds to the confusion over what constitutes appropriate labels, explanations, and treatments for these conditions *(3,5,31)* or even whether they are valid, reliable classification systems *(32)*. Dyspareunia and vulvodynia often are used interchangeably to describe a category of idiopathic vulvar pain conditions in the medical literature; however, the *psychiatric* use of the term dyspareunia refers to a specific sexual dysfunction rather than a category of idiopathic pain disorders.

The Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) continues to categorize idiopathic sexual pain conditions as psychiatric sexual dysfunctions *(33)*. This has sparked considerable nosological debate among researchers, many of whom argue that these conditions should be recategorized as pain conditions in future editions of the DSM *(11,13,30)*. The first of these sexual pain disorders, *dyspareunia*, is defined by DSM-IV-TR as recurrent or persistent genital pain associated with sexual intercourse in either gender. This is distinguished from *vaginismus*, which is defined by DSM-IV-TR as a sexual dysfunction of involuntary muscle spasms precluding vaginal penetration or intercourse, and often causing pain. According to the DSM-IV-TR model, dyspareunia is diagnosed when the disturbance is *not* fully attributable to a general medical condition, another Axis I psychiatric disorder (excluding sexual dysfunctions), vaginismus (i.e., involuntary contraction of the vaginal musculature preventing penetration), or insufficient vaginal lubrication in the female sufferer. Vaginismus is diagnosed when the disturbance is *not* attributable to a general medical condition or another Axis I psychiatric disorder (excluding sexual dysfunctions). Under this model, dyspareunia and vaginismus are each considered to cause marked distress or interpersonal problems in the sufferer.

The DSM-IV-TR further specifies subtypes of the sexual dysfunctions by three aspects of the problem's history: duration, specificity, and cause *(33)*. These type codes include *lifelong* versus *acquired* type, *generalized* versus *situational* type, and dyspareunia (or vaginismus) due to *psychological* factors versus *combined* psychological and medical factors. Vaginismus is often diagnosed in addition to the dyspareunia condition when pain is experienced *and* penetration is impossible. It should be noted that controversy remains over whether vaginismus even exists as an entity separate from dyspareunia because of the high rates of comorbidity for these conditions *(34–36)*.

The use of psychiatric categorization for idiopathic vulvar pain, as well as the negative stereotypes associated with this practice, can result in attribution errors such as *anchoring* and *confirmation bias (37)* in physicians' diagnostic pattern recognition. Misdiagnosis or dismissal of what appears to be a psychosomatic problem in these patients may occur as a result of these cognitive errors. Consequently, these patients are labeled as neurotic, frigid, or sexually repressed *(13)*, and their vulvar pain remains inadequately treated by the medical profession. This can be especially demoralizing or frustrating for women who functioned well, both emotionally and sexually, before their development of an idiopathic genital pain condition.

Understandably, this practice is distressing for women whose pain conditions lead physicians to classify their whole sexual being as "sick" *(11)*; it also underscores the

importance of improved public awareness of vulvodynia to facilitate proper diagnoses and medical care of vulvodynia patients. Another criticism of the use of psychiatric categorization for nonorganic, or idiopathic, sexual pain disorders is that it is *not* evidence-based; moreover, many of these patients report *no* clinically significant affective distress and often score within the normal range of functioning on psychological measures of anxiety, depression, and somatization *(19,23,38–40)*. Similarly, sexual functioning *may* remain possible for some women with vulvodynia, irrespective of their pain experience and severity *(14,34)*.

FEMALE GU PAIN AS CHRONIC PAIN DISORDERS

Dyspareunia, or painful intercourse due to a variety of causal factors, was originally described by Barnes in 1874 as a "condition of difficult or painful performance of the sexual function" *(41)*. It was then largely ignored for a century, until it appeared again in the literature as *burning vulva syndrome* in the 1980s *(41)*. As previously detailed, idiopathic genital pain disorders were subsequently viewed as either psychosomatic conditions or sexual dysfunctions.

In recent years, dyspareunia has been reconceptualized from a sexual dysfunction to a chronic pain disorder involving the genital region that results in interference with a patient's sexual functioning *(1,5,14,30,42,43)*. As previously mentioned, these authors have argued quite convincingly to assert that the DSM-V should reclassify dyspareunia as a pain disorder instead of a sexual dysfunction. Masheb et al. *(1)* further suggested that vulvodynia be differentiated into acute and chronic stages, to communicate information as to the duration of the illness in a particular patient. It should be noted that pain intensity in patients with female GU pain is generally reported as moderate to severe *(16)*; however, it is important to note that vulvar pain does not *always* preclude sexual activity in these women *(14,34)* and is *not* exclusively sexual in origin. It is often exacerbated by *any* pressure exerted on the vulva from exercise, sitting, walking, tampon or speculum insertion, and tight-fitting clothing, in addition to pain related to sexual intercourse *(44)*.

Pukall et al. *(45)* reviewed relevant studies on pain processing in patients with the form of idiopathic female GU pain known as vulvar vestibulitis syndrome (VVS). These authors reported evidence that the vulvar vestibules of these women have altered sensory processing, similar to sensory changes found in patients with other chronic pain conditions. Moreover, VVS patients reported pain sensations at the same level that healthy controls reported feeling touch, suggesting that VVS patients are more sensitive to any sort of physical contact. This finding was true both in the vestibular area and in other, non-genital regions of the VVS patients' bodies, suggesting that VVS patients have a more generalized pain condition or sensory abnormality than was previously believed. In a similar study, Granot et al. *(42)* found that VVS patients had lower systemic pain, lower pain thresholds, higher levels of physiological response to pain, and higher anxiety levels than controls. These authors also concluded that VVS is a *generalized*, rather than a localized, pain problem. Pukall et al. *(45)* supported this finding with functional magnetic resonance (fMRI) imaging in which neural activity in response to touch was examined in VVS patients and controls. VVS patients were found to be more sensitive to pain in general than were control subjects. This was also true of genital pain, in that VVS patients, when compared with controls, had more activation of brain areas important to pain processing when genital areas were stimulated.

One advantage to the widespread adoption of this paradigm shift would be that as a pain disorder, dyspareunia would be viewed as *multifactorial* in origin, like other chronic pain conditions *(1,22)*. For example, the fMRI findings of Pukall et al. *(45)* promoted this multidimensional understanding of vulvodynia, because both affective and sensory areas of the brain were activated during painful genital stimulation in VVS patients. As previously stated, Granot et al. *(42)* argued that VVS should be considered a *generalized* pain disorder as opposed to a localized (e.g., genital) pain disorder. Using PET scans and personality assessments, Granot *(46)* identified neurochemical mechanisms of the pain experience that are affected by personality traits in VVS patients. These personality traits, including harm avoidance, reward dependence, and novelty seeking, are related to altered neurochemical activity and pain perception in VVS patients, leading to overall enhancement of their pain sensitivity *(46)*. It was unclear, however, whether these psychological factors were a cause or effect of physiological changes inherent to VVS.

Others supporting a generalized pain disorder conceptualization of VVS include Lotery et al. *(3)*, who reported evidence that VVS patients have increased innervation of the vestibule, but it was not determined whether this was a cause or effect of the VVS. These authors also reported ratings of higher pain intensity in both the upper extremities and the vulvar vestibule in VVS patients, suggesting a generalized pain disorder. Green et al. *(47)* described VVS as an *atypical* pain disorder; furthermore, these authors proposed that VVS is part of an inflammatory, genetic pain syndrome that includes interstitial cystitis and irritable bowel syndrome, although the evidence was not conclusive. Kaler *(11,13)* promoted the notion that genital pain should be understood as a *functional* pain phenomenon rather than as a sexual disorder.

Kaler *(13)* also referred to the "dominance of heteronormativity," which this author described as a bias inherent to the disease model of female coital pain. In addition, Kaler argued that vulvodynia may or may *not* be attributable to underlying psychological problems, relational conflicts, or physiological causes—as is often the case in other chronic pain syndromes. Furthermore, some research suggests that it is the *chronicity*, or unrelenting nature of persistent vulvar pain, and *not* its severity, that accounts for psychological distress and disturbances in functioning *(32)*. Important treatment implications resulting from this model include focusing attention on alleviation of the pain itself in an effort to prevent psychological distress, rather than aiming treatment at uncovering any presumed, underlying physiological or psychological problems of the VVS patient *(28)*.

As the paradigm for understanding vulvar pain shifts from a sexual dysfunction to a chronic pain model, additional research is needed to determine the efficacy of chronic pain treatment methods applied to cases of vulvodynia, regardless of etiology *(1,31,43)*. Moreover, improved understanding of the psychological aspects of vulvodynia could lead to improved treatments, such as combining specific physiologic and psychological interventions for chronic pain conditions *(46)*. Under the chronic pain paradigm, implications for future research include development of vulvodynia treatments focused on the pain and its underlying mechanisms, rather than on the supposed psychosexual dysfunction of these patients. This shift in treatment focus may be especially valuable because it has been observed that some women with dyspareunia are able to maintain adequate sexual functioning, despite their experience of coital pain *(14,34)*.

Conversely, in those patients whose vulvar pain conditions preclude their enjoyment of sexual intimacy, Graziottin and Brotto *(25)* emphasized the importance of first

focusing treatment on eliminating or reducing the pain, and then re-establishing the ability of the VVS patient and her partner to enjoy their sexual relationship. Furthermore, the ability of future generations of physicians to discuss sexual concerns with patients is being enhanced by communications skills training now required in many medical schools *(48)*. As a result, it is likely that a majority of patients with GU pain conditions who previously may have suffered in silence will now receive the treatment they deserve.

DYSPAREUNIA (VULVODYNIA) AND ITS SUBTYPES

As previously noted, dyspareunia is often used interchangeably with vulvodynia in the medical literature, perpetuating the misunderstanding of these disorders *(31)*. Veasley and Marinoff *(49)* stated that it is critical for a precise classification scheme to be adopted in order to ensure that the scientific and clinical communities will consistently diagnose, research, and reference the vulvodynia conditions—and, it is hoped, eventually lead to consensus about etiologies and effective treatments. *Dyspareunia* will be distinguished from vulvodynia for the duration of this chapter and defined as pain associated with actual or attempted intercourse. *Vulvodynia* will be conceptualized as chronic vulvar or perineal pain experienced regardless of attempted intercourse, touch, or stimulation of the vaginal region.

Idiopathic vulvar pain was described in the medical literature as early as the late nineteenth century, although it largely went unnoticed until the 1970s when interest in vulvar pain resurfaced in the medical community *(50)*. A group of gynecologists, dermatologists, pathologists, and other professionals created the International Society for the Study of Vulvovaginal Disease (ISSVD) to study vulvar disease and idiopathic vulvar pain, which they named *burning vulva syndrome* in 1976. The ISSVD later changed the name of the disorder to *vulvodynia*, and described two subsets, *dysesthetic vulvodynia* (DV) and *vestibulitis (50)*.

Vulvodynia was first defined as a chronic vulvar discomfort characterized by the patient's complaint of burning, stinging, irritation, or rawness *(51)*. Dyspareunia (i.e., pain associated with intercourse) was *not* a consistent feature of vulvodynia under this definition, as the discomfort of vulvodynia often occurs without any stimulation or contact of the vulvar region. Vestibulitis was distinguished from vulvodynia by its focal (rather than diffuse) pain, entrance dyspareunia, and vestibular erythema. Other terms followed for vestibulitis, including *vestibular adenitis (52)*, *focal vulvitis (53)*, and VVS *(44)*. The ISSVD then presented a taxonomy which separated vulvodynia into categories of vulvar pain syndromes and vulvar dermatoses *(54)*, which occurred either alone or in conjunction with each other. McKay *(55)* further delineated five diagnostic patterns of vulvodynia, including: vulvar dermatoses, infections, iatrogenic factors, vulvar vestibulitis and dysesthetic "essential" vulvodynia.

The ISSVD 1999 World Congress narrowly voted to change the terms to *generalized vulvar dysesthesia* (from DV) and *localized vulvar dysesthesia, vestibulodynia* (from VVS). The ISSVD 2001 World Congress again changed the nomenclature to *spontaneous vulvar dysesthesia* and *provoked vulvar dysesthesia*, both of which could be localized (e.g., to the vestibule) or generalized. Most recently, the 2003 ISSVD World Congress appointed a committee to revisit this issue because of a general dissatisfaction with the 1999 and 2001 categorizations of vulvar pain disorders *(49,50)*.

The current 2003 ISSVD classification of vulvar pain includes *vulvar pain related to a specific disorder* (e.g., infectious, neoplastic, inflammatory, or neurologic

types); *generalized vulvodynia* (involving the entire vulva); and *localized vulvodynia* (involving a portion of the vulva) which includes vestibulodynia. Vulvodynia was further specified as "provoked," "unprovoked or spontaneous", and "mixed", to denote the presence or absence of contact or stimulus associated with the pain. Under this classification system, VVS was renamed "provoked vestibulodynia" and DV was renamed "generalized vulvodynia" *(49,50)*; although, to date, this terminology has not been widely adopted in the literature. For the purposes of this chapter, the terms DV and VVS will be maintained as they are the most prevalent terms in the literature.

As noted by Schmidt et al. *(39)*, vulvodynia is a "complex, multifactorial clinical syndrome (p. 378)" with a confusing interrelationship of factors influencing its subtypes *(55)*. In the differential diagnosis of vulvodynia subtypes, it is important to note the patterns of discomfort and the anatomic areas involved in the presentation *(55)*. It is also important to distinguish between presentations with objective, physical findings and those with no physical evidence of vestibulitis or cutaneous changes *(39)*. For the purposes of this chapter, three major subtypes of vulvodynia will be considered. These include: (1) the organic vulvodynias, (2) DV, which is also known as "idiopathic," "essential," or "generalized" vulvodynia, and (3) VVS, which is also known as "localized" vulvodynia or dysesthesia.

Organic vulvodynias are thought to originate from various organic causative factors implicated in vulvar pain *(13)*. These factors include infective (e.g., bacterial, viral, microbial), genetic, traumatic or iatrogenic (e.g., chemotherapy, steroid treatment, physical injury, or trauma from laser treatments), irritational (e.g., use of soap, antiseptics, or oral contraceptives that reduce protective mucus), allergic (e.g., hypersensitivity to allergens, contact dermatitis), dermatoses, neoplastic lesions, neurological (e.g., pudental nerve damage), hormonal (e.g., cyclic, menopausal), vascular injury, and altered central neuronal processing *(24,28,55,56)*. Treatments prescribed for the organically induced vulvodynias (as detailed in earlier chapters of this text) typically address the physiological or medical issues underlying the pain, with little attention paid to psychosocial considerations.

DV, which is also known in the relevant literature as *idiopathic* or *essential vulvodynia, vulvar dysesthesia*, or, most recently, *generalized vulvodynia*, is a "diagnosis of exclusion" *(57)*. Its typical presentation includes the complaint of "constant unremitting vulvar burning in a diffuse pattern, usually over the entire surface of the inner labia" (*(55)*, p. 430). Although the patients diagnosed with DV rarely report dyspareunia, they often complain of rectal or urethral discomfort in addition to the vulvar burning. DV patients are usually postmenopausal, often middle-aged to elderly, and may suffer for many years with this condition. Although the cause is unknown, a neurological problem related to "damaged sensory nerves or an altered perception of sensation" is suspected (*(55)*, p. 430). Others suggest that a sympathetically maintained pain loop is responsible for this condition, because the most effective therapy for DV has been a low-dose treatment with amitriptyline or another tricyclic antidepressant *(3,31)*.

VVS, which is also known in the relevant literature as *localized dysesthesia, localized vulvar dysesthesia*, or, most recently, *localized vulvodynia* or *provoked vestibulodynia*, is the leading cause of dyspareunia in premenopausal women and is present in as many as 15% of cases presenting to outpatient gynecological clinics *(26,58)*. In addition, patients diagnosed with VVS are usually between the ages of 20 and 45 years old, and tend to be younger than those diagnosed with DV *(44)*. The pain in this type of vulvodynia is restricted to the vulvar vestibule or the inner portion of the vulva. VVS

is a "chronic, persistent clinical syndrome characterized by severe pain on vestibular touch or attempted vaginal entry, tenderness to pressure localized within the vulvar vestibule, and physical findings confined to vestibular erythema of various degrees" (*(55)*, p. 428). VVS originally was characterized by Friedrich *(44)* as severe pain on attempted vaginal entry, or on vestibular touch or pressure, with no evidence of vulvar pathology, except for erythema (i.e., inflammation and variable reddening of the vestibule). Because erythema is not present in all cases, it has been the subject of debate as to whether it should remain a defining characteristic of VVS *(25,47,59)*; nevertheless, the diagnosis of VVS is still based on Friedrich's *(44)* criteria and includes erythema.

McKay *(55)* stated that biopsies of the vestibule are *not* helpful in diagnosing VVS, although surgical removal of the affected portion of the vestibule often results in alleviation of the pain. The diagnostic test for VVS is performed by applying pressure to areas of the vestibule with a cotton swab, a procedure recently standardized with a spring-loaded device known as a *vulvalgesiometer (60)*. Etiology and pathophysiology of VVS pain are still unclear, but are hypothesized to be multifactorial in nature, including infectious, vascular, muscular, neurologic, genetic, and psychological causes *(28,61)*. VVS pain may persist for months or years, and it may remit spontaneously in some cases. Use of topical 5% lidocaine ointment and lubricants may allow patients with VVS to tolerate touch or sexual activity. After numerous treatment options have failed to alleviate the pain, surgical excision of vestibular tissue is often helpful for cases in which the pain has persisted for more than a year *(55)*.

Because no physiological or organic cause can be found in a majority of vulvodynia cases, this can lead treatment providers wrongly to assume that the patient's problem is psychological in origin. Once organic etiologies are ruled out, patients' vulvodynia conditions are then diagnosed according to the location and quality of the experienced pain. The remainder of this chapter will address the vulvodynias without a known etiology: DV and VVS. It should be noted that, regardless of etiology, vulvar pain is responsible for numerous effects on the lifestyle of its sufferers. This can include impairment in women's emotional well-being as well as in their ability to perform routine activities such as walking, sitting, exercise, and sexual activities *(32,56)*. Thus, the negative impact of vulvar pain is, at any given point in time, significant in the lives of thousands of women across age, race, and socioeconomic dimensions *(2)* and should be aggressively researched and treated until satisfactory outcomes, if not a better understanding of etiology, are achieved.

PSYCHOSOCIAL FACTORS IN IDIOPATHIC FEMALE GU PAIN: DV AND VVS

Metts *(56)* described vulvodynia, including DV and VVS, as a syndrome of unexplained vulvar pain, which is often accompanied by physical disability, reduced performance of daily activities, dysfunction in sexual relations, and psychological distress. Historically, vulvar pain without a known organic etiology was considered psychosomatic in origin *(9,16)*; conversely, the recent literature indicates there is *no* good evidence supporting a purely psychogenic explanation either for DV *(19,23)* or VVS *(23,38,47)*. It should be noted that agreement *is* reported in the recent literature that vulvodynia in general *(43)*, and VVS in particular *(23,38)*, interfere with patients' sexual functioning and are best classified as circumscribed pain disorders.

Furthermore, although numerous studies have linked various types of psychological disturbance to vulvodynia *(15,18,62)*, no consensus exists as to whether vulvodynia patients are more emotionally distressed or disturbed than controls *(38)*. It is also unclear as to whether psychological difficulties, when found in patients with unexplained vulvar pain, are the *causes* or *effects* of the vulvodynia condition *(3,18,22,39,46)*. Some authors have reported similarities among DV patients in their psychological profiles *(39,62)* and have concluded that DV patients are more psychologically disturbed than VVS patients. There is no clear indication, however, that women with VVS share a distinct psychological profile or a tendency toward psychological disorders such as somatization, anxiety, or depression *(38–40)*.

For example, Aikens et al. *(19)* found that patients with chronic vulvar pain because of DV or VVS reported more intense depressive symptoms than did controls on the Beck Depression Inventory (BDI), a commonly used measure of clinical depression *(63)*. Interestingly, the overall BDI scores of vulvodynia patients did *not* indicate a higher incidence of clinical depression in these patients. The BDI scores of the vulvodynia patients in this study were found to be inflated because of an overlap of somatic symptoms of depression and the symptoms of vulvodynia itself. Although their *somatic* symptoms of depression *were* higher than controls, these vulvodynia patients reported no greater levels of either the *cognitive* or the *affective* symptoms of depression. Therefore, this finding suggests that the BDI scores of vulvodynia patients were increased merely by reporting the somatic effects of their illness (e.g., reduced libido) on quality of life. Aikens et al. *(19)* suggested that the lack of both cognitive-affective symptoms and clinical severity levels of depression in these vulvodynia patients challenged earlier findings that supported psychogenic explanations for idiopathic vulvar pain *(15–17)*. Aikens et al. *(19)* proposed instead that the somatic symptoms reported by their VVS patients reflected the effects of chronic pain and its resultant disability on their quality of life, as opposed to resulting from an actual depressive disorder or psychogenic source of their vulvar pain.

These results reported by Aikens et al. *(19)* were in marked contrast to the earlier findings of Jantos and White *(15)*, who reported BDI scores of VVS patients indicating that the majority were clinically depressed (89%) or suicidal (57%). Jantos and White *(15)* observed that a majority of their VVS patients also had tendencies toward perfectionism, anxiety, headaches, low sexual desire, and reduced sexual activity. It is important to note, however, that these authors did *not* equate VVS with a somatoform disorder and cautioned providers to make conservative interpretations of any findings of somatization tendencies in VVS patients. In contrast, Schover et al. *(17)* and Lynch *(16)* suggested a stronger link between the psychological problems of VVS patients and their vulvar pain, and advocated for a combination of psychological and surgical treatment to ensure successful outcomes in VVS patients.

Other psychological components of VVS are also evident from recent research. For example, VVS patients were found to have a lower pain threshold, a higher estimation of pain, and catastrophizing thought patterns related to intercourse, as well as higher levels of trait anxiety, somatization, and negative body image in studies comparing them with both other chronic pain patients and controls *(26,29,42)*. Similarly, Payne et al. *(64)* proposed an interesting link in VVS patients between anxiety, fear of pain, and hypervigilance to coital pain. These authors attributed the coital pain and decreased sexual function evident in VVS patients to their heightened pain awareness and resultant distraction from sexually arousing stimuli during intercourse. Payne et al.

(64) recommended that VVS treatment should include refocusing the patient's attention during sexual activity *toward* sexually arousing or pleasurable stimuli, and *away* from pain processing. This process of refocusing the patient's attention during sexual activity was found to increase *both* sexual function and satisfaction in VVS patients.

In another study of psychosocial factors of VVS, Danielsson et al. *(65)* reported that VVS patients were more likely than controls to experience somatic complaints, feel abandoned by someone close to them, feel unable to speak intimately with a close friend, and engage in sexual activity when they really did not want to. It was noted by these authors that VVS patients differed very little overall from healthy controls in both their psychosocial and their sexual backgrounds. For example, sexual abuse, although very commonly reported in patients with chronic pelvic pain and somatization disorders, was found to be no more prevalent in patients with DV or VVS than in controls *(3*, *21–23*, *65)*.

In a recent review, Green and Hetherton *(38)* researched and compared all articles published during the previous decade that examined the psychosocial aspects of VVS. Overall, these authors found no consensus about specific behavioral patterns or differences in psychological functioning in VVS patients as compared with that in controls. Green and Hetherton *(38)* reported that some studies included in their review found higher levels of psychological distress, state or trait anxiety, depression, somatization, marital distress, and sexual dysfunction in VVS patients; however, significant life stressors often coincided with the onset of VVS pain in these patients and may have confounded the results. Other studies reviewed by these authors found that VVS patients were generally well adjusted and did *not* meet criteria for a diagnosis of somatization disorder; furthermore, these VVS patients reported average levels of marital satisfaction and had relationships with psychologically healthy partners. Although there was no consensus in the recent literature regarding psychological illness in VVS patients, Green and Hetherton *(38)* concluded that VVS interferes with sexual functioning, even to the point of sexual dysfunction in some patients. This conclusion further supported other findings that *marital* satisfaction was *not* affected for vulvodynia patients and their partners, although *sexual* function *was* reduced in couples where vulvodynia was present *(23,40,43)*.

Personality and psychophysical characteristics have been found to differentiate women with *primary* (i.e., present since the first sexual experience) versus *secondary* (i.e., acquired after a period of normal sexual functioning) VVS. Granot et al. *(66)* reported that women with primary VVS had higher rates of trait (i.e., enduring, characterological) anxiety, pain perception, and sympathetic nervous system arousal than those with secondary VVS. These characteristics are commonly found in patients with other types of chronic pain (e.g., lower back pain), as well. Granot et al. *(66)* proposed that these findings suggested etiological differences in primary versus secondary VVS. Secondary VVS was attributed to local vulvar pathology, whereas primary VVS was attributed to a combination of psychophysiological factors and vulvar pathology. Accordingly, these authors posited that different subsets of VVS may respond differently to various treatment approaches and recommended further research into this area.

In summary, although various studies have linked DV and VVS to psychological disturbance, there is no *consistent* evidence that vulvodynia patients are more disturbed psychologically than controls or that they are more likely to have been abused. Furthermore, studies examining the correlation of psychological disturbance with idiopathic vulvar pain have been unable to ascertain the direction of the causal

relationship between these conditions. As is true of other chronic pain conditions, anxiety and depression may result from vulvodynia's unremitting symptoms, its resultant physical or sexual disability, relationship disturbances, or misunderstanding by others.

Although it is not surprising that psychological distress often results in patients suffering from vulvodynia, it is not clear whether psychological factors contribute to the development of DV or VVS in these patients. Treating physicians adhering to a biomedical model and finding no physical evidence of a disorder may unwittingly communicate to the patient that the problem is "all in her head" *(56)*, thereby invalidating her pain and increasing the patient's distress. It is important to note that recent studies indicate that vulvodynia does *not* appear to be a psychosomatic condition *(19,47)* and should *not* be considered or treated as such. Although there is no compelling evidence for a psychogenic cause of vulvodynia, it is often accompanied by significant psychological distress in its sufferers. Therefore, this distress should be understood from a biopsychosocial perspective and addressed in a comprehensive, if not multidisciplinary, treatment program designed specifically for patients with chronic vulvar pain.

PSYCHOSOCIAL STRATEGIES IN MULTIDISCIPLINARY TREATMENT OF FEMALE GU PAIN

According to the *biopsychosocial (67)* understanding of chronic pain, psychological factors contribute to the perception and perpetuation of pain; therefore, it follows that these factors can be used to moderate the pain *(68)*. In contrast to the traditional biomedical model, which is based on mind–body dualism, the biopsychosocial model focuses on the complex interplay of biological, psychological, and social factors that contribute to an individual's illness experience. Pain is considered a *subjective* experience under the biopsychosocial model and is seen as a result of sensory input being filtered through a person's prior learning history, genetic composition, sociocultural background and beliefs, physiological status, cognitive appraisals, emotional state, and expectancies *(29,68)*. As a result of this interplay, the experience of chronic pain encompasses not only physical pain sensations but also includes cognitive preoccupation with suffering, the sick role, catastrophic beliefs, and decreased self-efficacy; behavioral limitations of daily activities in social and work domains; behavioral increases in the use of medications or health care services; and affective components of mood disturbance such as hopelessness, depression, or anxiety *(29,68)*.

This conceptualization of pain is thought to be true of vulvodynia *(14,69)*, where cognitive, sensory, affective, and interpersonal factors are believed to influence each other and cause additional pain in what Pukall et al. *(69)* labeled a "vicious cycle" of chronic vulvar pain. Thus, a thorough assessment and interdisciplinary treatment plan for vulvodynia should include attention to pertinent medical, social, and psychological issues to maximize chances of therapeutic success *(70)*. The role of the psychologist is vital in the multidisciplinary approach to vulvodynia treatment, because any chronic pain condition is a major stressor that can impinge on a patient's emotional health and daily functioning. Psychologists often provide the following information for the multidisciplinary team treatment of vulvodynia: assessment of patients' psychosocial functioning, personality characteristics, social supports, motivational status, and coping

resources *(71)*. This information allows the team to plan and provide treatment tailored to the specific psychological needs of each patient.

In addition, Graziottin et al. *(28)* suggest strategies for *pain mapping* and for taking a thorough past and present history of the pain. This mapping technique is the recommended starting point for an enlightened, multidisciplinary approach to vulvodynia treatment, because it validates the patient's pain experience by making her pain the focus of clinical attention; furthermore, it does so *without* implying that the pain is psychological in origin *(11,28)* or focusing exclusively on the sexual activity with which the pain interferes *(14,43)*. It is important to note that the pain map is created with the patient's input in order to correctly detail the patient's experience of vulvar pain. The pain map includes pain onset and its characteristics, location, intensity, duration, and quality of response to medications; impact on sexual and daily activities; pain perception and how the patient experiences the pain and its meaning; sexual history, including STDs, contraception, protection used to prevent STD, frequency and repertoire of sexual activity, and presence of intercourse; history of genital trauma or sexual abuse; and personal habits or activities, such as frequent washing, douching, type of hosiery or underwear, and contact sports that could worsen genital pain. Not only does this comprehensive discussion of the patient's pain experience serve to validate the patient's subjective pain experience, it makes vulvar pain the focus of clinical attention and treatment planning *(28)*.

Binik et al. *(14)* also include in their vulvodynia assessment a list of activities aside from intercourse that elicit the pain, as well as questioning the patient about the personal meaning, or attribution, of her pain. Specific questions about the presence of pain itself, as well as questions about disruptions in the patient's sexual response cycle, coital frequency, interpersonal relationships, and methods for coping with vulvar pain are also included in a thorough assessment *(14)*. The multimodal treatment approach for vulvodynia *(25,28)* emphasizes the importance of using a pain management framework for treatment, because it becomes a chronic condition unless diagnosed and treated in its early stages. A variety of factors, including psychological issues, pelvic floor dysfunctions, infections, and negative sexual experiences, neurogenic and psychogenic causes are implicated in the development of vulvodynia *(18)*. Chronic pain from the urogenital region may then spread to other areas, creating secondary pain syndromes through a central mechanism of pain regulation through the spinal cord and pelvic nerves *(27)* unless its progression is halted.

Sexual functioning should also be addressed in the assessment interview, as chronic vulvar pain often leads to disturbance in sexuality and intimate relationships *(62,69, 72,73)* and resolution of the pain itself does *not* guarantee the restoration of patients' sexual or daily functioning *(69)*. Pukall et al. *(69)* emphasized that although vulvodynia is best classified as a pain disorder, the sexual dysfunction that accompanies this pain condition is often the primary treatment concern for patients. Therefore, the primary functional goal of treatment often is restoration of sexual intimacy, as opposed to pain reduction, in such patients. A detailed sexual history *(14,34)*, similar to Graziottin's pain map *(28)*, is essential to the information-gathering process in multidisciplinary vulvodynia treatment. An effective clinician will perform a detailed sexual history of the patient, including a timeline of the development of the painful condition, its circumstances, trauma history, and current relationship satisfaction.

Formal psychological assessment using comprehensive personality assessment instruments also provides objective information about the patient's psychological

functioning and how their emotional state may be influencing their pain experience. Because many studies have used abbreviated forms of personality instruments, it would be useful in future studies to determine whether the use of complete versions of these instruments (e.g., the MMPI-2 and the Personality Assessment Inventory or PAI) are recommended for use in future research *(74,75)*, because other studies using less comprehensive assessment tools have yielded equivocal results about patterns of psychological disturbance or distress in vulvodynia patients. The Pain Patient Profile (P3) by Tollison and Langley *(76)* is also recommended for future research to assess anxiety, depression, somatization, and coping styles of vulvar pain patients as compared with other patients experiencing chronic pain conditions.

Enhancement of patients' coping skills, self-efficacy expectations, and muscle relaxation skills are common psychotherapy goals in the treatment of chronic pain. Coping skills training is a useful component of psychological treatment for chronic pain of any type, because *passive* coping strategies (e.g., limiting activities, relying on a caregiver, embracing the sick role) are related to increased pain and depression; conversely, *active* coping strategies (e.g., distraction, ignoring pain, and engaging in meaningful activity) are known to promote adaptive functioning in chronic pain patients despite their continued experience of pain *(68)*. Improvement of coping techniques and stress reduction strategies through psychotherapy is often helpful for pain patients; this is especially important for patients whose vulvodynia symptoms occur during times of stress *(17)* or whose psychological distress results from the experience of relentless vulvar pain *(8)*. Patients' ability to cope with chronic vulvar pain may also be enhanced by engaging in relationships with supportive partners, support groups, religious faith, and meaningful distractions such as hobbies *(21)*.

Cognitive errors such as *catastrophizing* (i.e., the anticipation of negative or aversive outcomes coupled with minimization of one's coping abilities) during painful stimulation decrease patients' pain tolerance, elevate their emotional distress, and promote disability *(29,68)*. Psychologists routinely employ cognitive behavioral therapy (CBT) techniques to allow patients to address the negative emotional aspects of chronic pain (e.g., depression, anxiety, or anger); furthermore, CBT techniques are used to challenge any distorted or irrational thoughts and beliefs that may be exacerbating their pain experience or reducing their feelings of self-efficacy *(26)*. For example, Granot and colleagues *(29,42)* promote the use of psychological interventions that challenge counterproductive thought patterns and body image disturbances in vulvodynia patients; furthermore, these authors consider CBT interventions as essential to the successful multidisciplinary treatment of VVS.

Vulvodynia patients with anxious and somatizing tendencies often display a heightened awareness of body sensations and may attribute them to catastrophic disease. Payne et al. *(64)* suggested a multimodal treatment approach for VVS, targeting fear and anxiety as they relate to intercourse, as well as hypervigilance for coital pain. Although not common in practice, an interdisciplinary, multimodal treatment program for vulvodynia is ideal, where a variety of specialists (e.g., physicians, psychologists, physical therapists) assess the different aspects of the vulvar pain (e.g., neurological, interpersonal, affective, muscular) to develop a coordinated treatment plan *(14)*.

Included in the multimodal approach to treatment are psychotherapy and alternative treatments *(18)*. These promising treatments aim to reduce patients' anxiety and resultant muscle tension through stress management, relaxation training, exercise, physiotherapy *(77)*, acupuncture *(78)*, eye movement desensitization (EMDR) *(65)*, and

hypnotherapy *(79)*. Cognitive restructuring may also reduce sexually related anxiety in VVS patients by addressing their maladaptive behaviors, beliefs and concerns, when present. Sex therapy utilizing a multimodal approach *(80)* has been successful in treating vulvodynia through addressing individual, couple and medical issues related to the patient's presenting problem of vulvar pain. Psychotropic treatment with tricyclic and other antidepressant medications, as well as anticonvulsants, also benefits many vulvodynia patients *(3,62,81,82)* by reducing both psychological distress and pain perception. Although vestibulectomy surgery for VVS is the treatment with the best documented outcomes, it is not usually tried until more conservative treatment options have failed *(47)*.

Biofeedback historically has been used to reduce the negative effects of muscle tension on chronic pain. Although there have been relatively few studies conducted to examine the efficacy of these treatments with chronic GU pain, electromyographic (EMG) biofeedback of the pelvic floor musculature has been used successfully to treat VVS *(59,83)*. In Glazer's *(83)* seminal study, the majority of VVS patients reported significant pain reduction and successful resumption of sexual intercourse at the end of 16 weeks of treatment with EMG biofeedback. This finding is particularly encouraging because pain is the chief complaint of most vulvodynia patients and is the primary factor responsible for their problems with sexual functioning *(21)*. Of the 428 women reporting their experience with DV or VVS in response to a web-based survey, a majority stated that vulvar pain negatively affected their libidos and their enjoyment of sexual intercourse. These women reported that an understanding partner, support groups, hobbies or distractions, and faith or religion improved their ability to cope with the chronic pain. Most notably, medical professionals were *not* viewed as a source of emotional support or pain relief for a majority of these patients *(21)*. It should be emphasized that the experience of an empathic, validating doctor–patient relationship in itself is an integral part of a healing experience for patients with vulvodynia *(4)*. This is especially true because many patients' complaints and suffering have been repeatedly minimized or even misdiagnosed *(37)* by treatment providers who are insensitive or unskilled at vulvodynia treatment.

In summary, it is essential in the assessment phase of vulvodynia treatment, for the treating clinician to gather patients' sexual history information in a collaborative, nonjudgmental, and validating manner. This practice will help to ensure an accurate clinical diagnosis and lead to appropriate, individualized treatment of vulvar pain and related sexual dysfunctions. Ideally, the clinical assessment of vulvodynia also includes a detailed psychosocial assessment that integrates the patient's sexual history with the chronic pain assessment. It also incorporates information gleaned from the traditional psychosocial history, objective personality-assessment results, chronic pain inventories, and sexual functioning questionnaires, when appropriate. This holistic, multimodal approach incorporating gynecological, rehabilitative and psychological interventions is recommended by Graziottin et al. *(25,28)* in the treatment of vulvodynia, which they consider a multifactorial syndrome involving biological, psychosexual, and relational issues.

Practical guidelines detailing comprehensive, multidisciplinary treatment approaches for vulvodynia recently have been published elsewhere *(5,81,84)* and are highly recommended readings for treatment providers and patients alike. These treatment guidelines outline integrated medical, surgical, pharmacological, and alternative treatment therapies to address both DV and VVS forms of idiopathic gynecological pain.

Strategies to be used by psychologists working with this specific subset of chronic pain patients are also recommended. Once all relevant medical issues have been addressed or ruled out in patients with vulvodynia, clinical attention should then focus on any psychological, relational, and sexual issues impinging on the GU pain *(4,25,34,80,85)*.

It is anticipated that accurate diagnosis and early treatment of vulvodynia will become more prevalent as public awareness improves and consensus is attained in the definition and clinical management of vulvodynia *(5)*. Following this enlightenment, it is hoped that the stigmatization and misattribution of idiopathic vulvar pain will decrease; accordingly, it is also hoped that availability will increase for these patients to effective, holistic treatments in multidisciplinary clinics using a chronic pain treatment approach for vulvodynia.

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IV Treatment Perspectives for the Management of Genitourinary Pain

20 CP/CPPS Pelvic Floor Dysfunction

Evaluation and Treatment

Rhonda K. Kotarinos, PT, MS

SUMMARY

Conservative management of pelvic floor dysfunction (which includes pain with and without urinary symptoms, and incontinence problems) has a 30–70% success rate. Traditionally, the conservative management approach has addressed the pelvic floor from the point of weakness or excessive tone. A nuance of the pelvic floor that has not been previously addressed with pelvic floor therapy is the concept of a shortened pelvic floor. A shortened pelvic floor can appear weak and there may be excessive tone. But there is a point where the increased electrical activity abates and the pelvic floor is left in a shorted state.

The primary goal of pelvic floor therapy is control and coordination of the pelvic floor musculature with strengthening being a secondary goal. To treat a short pelvic floor, the clinician must first recognize the condition and then appropriately treat it. Once the length of the pelvic floor is normalized, the primary goals of control and coordination can be achieved setting the foundation for strengthening.

KEY WORDS: Shortened pelvic floor; Trigger points; proprioceptive neuromuscular facilitation; chronic pelvic pain; myofascial manipulation.

CONTENTS

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INTRODUCTION

Pelvic pain syndromes have no gender bias. Traditionally, pelvic pain was thought to be a problem experienced only by females and usually within their reproductive years. Various diagnoses are ascribed to female pelvic pain. They include painful bladder syndrome/interstitial cystitis, vulvodynia, vulvar vestibulitis, urethral syndrome, irritable bowel syndrome, and levator ani syndrome to name a few. Some form of chronic pelvic pain affects up to 15% of the female population in both the United States and the United Kingdom *(1,2)*. In the United States, this means that over 9 million women experience some form of pelvic pain *(1)*.

Prostatitis, affecting 2–10% of men worldwide, is the most common diagnosis associated with male pelvic pain *(3)*. According to the National Institutes of Health, 90–95% of the males who have symptoms are classified as chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) *(3)*. The most common symptoms associated with CP/CPPS are genital or pelvic pain coupled with urinary complaints and/or sexual dysfunction. To be given a diagnosis of category III prostatitis, pelvic pain is a required symptom. Pelvic pain may be expressed in the perineal, suprapubic, rectal, coccygeal, urethral, testicular, or scrotal regions. Frequency, dysuria, incomplete emptying or a sense of post-void fullness are the common urinary complaints associated with CP/CPPS. Sexual complaints include decreased quality of erections, decreased ejaculatory satisfaction, or pain with ejaculation.

Research to explain the etiology and management of pelvic pain in both genders has been fraught with great frustration. It is interesting that the research of chronic pelvic pain syndromes in both populations has the pelvic floor musculature evolving as a significant component in its etiology and management. A recent review of urologic and non-urologic literature indicates that the prostate is not central to the symptoms. The more conceivable sources of the frustrating symptoms of prostatitis are musculoskeletal pain, pelvic floor dysfunction, myofascial pain syndromes, or functional somatic syndromes *(4)*. Over 14 years ago in a series of case studies, it was determined for females "that before extirpation of pelvic visceral organs is considered. . . .The pelvic muscular element, which could well be the source of pain, must be evaluated" *(5)*. Ever so slowly the wheel turns, but thankfully, it is turning.

Finally, research is supporting exactly what was suggested 14 years ago. According to Zerman et al. *(6)*, pelvic floor myofascial pain syndromes and elevated pelvic floor tone limiting pelvic floor relaxation was found in almost 90% of their CP/CPPS patients. Myofascial trigger points and other musculoskeletal dysfunctions are being diagnosed more frequently in both men and women who seek care for their pelvic pain syndromes *(7–10)*.

Success rates range from 30 to 70% for decreasing pelvic pain symptoms by treating the documented myofascial dysfunctions *(7–10)*. Why is there only a 30–70% success rate? Is there a missing component to the evaluation and treatment of this patient population? The standard approach addresses the pelvic floor from the stand point of either weakness or excessive tone. An alternative perspective would be that the pelvic floor is stuck in a shortened state *(11)*. The key is to determine during the evaluation whether the patient has a pelvic floor that is weak and long or one that is weak and short. Once that has been determined, the treatment plan can be developed accordingly. Assessing and managing a weak and long pelvic floor is well established in the literature. Evaluation and treating the short pelvic floor will be described with in this paper.

MATERIALS

The evaluation of a patient presenting with chronic pelvic pain involves several broad categories of assessment. They include a standard extra-pelvic musculoskeletal examination, a soft tissue evaluation, a trans-vaginal/trans-rectal manual, and instrumented exam. An instrumented pelvic floor assessment can be accomplished with either pressure or electromyographic biofeedback. The standard extra-pelvic musculoskeletal examination is common practice among all physical therapists who treat pelvic floor dysfunction. Generally, this includes utilization of pain-mapping diagrams, gait observation, postural screening, range of motion of the trunk and lower extremities, an orthopedic assessment of the relevant joint structures, and a strength/length assessment of the major muscle groups of the lower quadrant. The nuances of the evaluation process that allow a physical therapist to determine whether the pelvic floor is short will be discussed herein. The treatment process to lengthen the pelvic floor resolving the patient's symptoms and enabling the patient to regain normal function of their pelvic floor will also be discussed.

METHOD

In order for a clinician to determine whether a pelvic floor is short, he must first believe that there is a possibility that such a situation can occur. Once this concept is ingrained in the mind of the clinician as being within the scope of possibilities, it then takes experience to make the diagnosis. To accept the idea of pelvic floor shortening one must understand how that it might occur. As always, we do not know what comes first, the chicken or the egg. To speculate, let us say that a patient has a culture proven infection. This may be vaginal, bladder, or prostate. With an infection, there is pain, urge or both. This causes the patient to put the pelvic floor into a state of active shortening. Eventually this leads to shortening without electrical activity. As the pelvic floor shortens, it compromises its ability to function in its normal reflex or active capacity.

Muscle physiology states that force generated by a muscle is dependent on the length of the muscle. Force generated by a muscle decreases on either end of the spectrum of the optimal length *(12)*. If the muscle is excessively long or short, there is decreased force generation. Therefore, as the pelvic floor shortens as a result of adaptive/protective shortening its function is compromised.

Now that the clinician accepts the concept of a short pelvic floor, making the diagnosis starts with the intake history. The complaint of frequency and urgency may be the first indicator to consider that there may be a short pelvic floor. Various professions tend to predispose people to short pelvic floors: teachers, nurses, assembly line workers, bus drivers, etc. With various work situations, it may not have been an infectious process that put them into adaptive shortening, but the fact that they have to chronically suppress their urges.

A short pelvic floor may be diagnosed with either a manual or an instrumented intra-pelvic examination. When doing the manual assessment, the active contraction palpated will be perceived as weak. But this weak contraction on palpation feels significantly different from that of a pelvic floor that is weak and long. The quality of the contraction of a short pelvic floor would be described as short and jerky with definite decreased range of motion and force. The substitution pattern is also different than that of the weak and long pelvic floor. During the active contraction of a weak,

lengthened pelvic floor, the patient tends to recruit the abdominal, adductor, and gluteal muscles. With the active contraction of a short pelvic floor, the patient's substitution pattern may include elevation of their rib cage and shoulders as their body is sliding cephlad on the table.

Another indication of a short pelvic floor is the quality of the post-shortening contraction relaxation. After an active shortening contraction of the pelvic floor there is relaxation to its previous resting position. In the patient with a short pelvic floor, the return to the resting position may not be felt by the examiner or the patient. The patient's proprioception for the shortening contraction is usually intact, but may not be for the post-shortening relaxation. Post-shortening relaxation may decreased or non-existent.

Instrumented evaluation of the pelvic floor can be accomplished with either trans-vaginal or trans-rectal surface electromyography or pressure measurement/biofeedback. With adaptive shortening the muscle shortens actively. As time passes the muscle stays shortened, but becomes electrically silent, having passed from an active to an inactive state *(13)*. This clinician has found that pelvic floor pressure measurement/biofeedback is better at documenting a short pelvic floor than surface electromyography. When vaginal-rectal pressure measurements are being utilized to assess pelvic floor function, the clinician must be sure that there is a simultaneous inward movement of the pressure probe during the contraction *(14)*.

The graphic profile of contractions generated by a weakened pelvic floor is usually of a bell-shape curve. Pressures increase gradually as the patient learns how to maximally contract and release, then gradually decrease as the pelvic floor fatigues (Fig. 1a). The patient with the short pelvic floor will demonstrate their peak pressures with their first and second contractions, and then their pressures gradually decrease over the next six to seven contractions (Fig. 1b). The rapid decrease in force generation with repeat contractions is consistent with a short pelvic floor.

Management of the patient with pelvic floor dysfunction creating symptoms of pain, frequency, and urgency begins with addressing the general musculoskeletal dysfunctions noted on the evaluation. Optimal functioning of the pelvic floor is not possible in the presence of a significant diastasis or an extremely weak abdominal wall. Closure of the diastasis is critical to the rehabilitation of the pelvic floor (Fig. 2). External stabilization with an abdominal binder, to be worn daily, may be utilized to facilitate closure if the diastasis is large: greater than 4 cm. Once the diastasis has closed, the patient is then managed with a comprehensive progressive abdominal strengthening program. To decrease the risk of creating or aggravating abdominal trigger points, standard abdominal strengthening should be avoided until a diastasis has resolved. Trigger points in the abdominal musculature can be instrumental in creating urinary symptoms *(15)*.

Manual therapy should be used to address myofascial and connective tissue restrictions. In an established viscerosomatic/somatovisceral reflex, there can be alterations in the connective and muscular tissues in the reflex referral zone. Connective tissue changes associated with a viscerosomatic/somatovisceral reflex are as a result of trophic alterations and include vasoconstriction, increased thickening of the skin, and subcutaneous tissue. Muscle changes can include localized muscular contraction causing hardening, tension and hypersensitivity. Trigger points can also develop in the muscles associated with the referral zone.

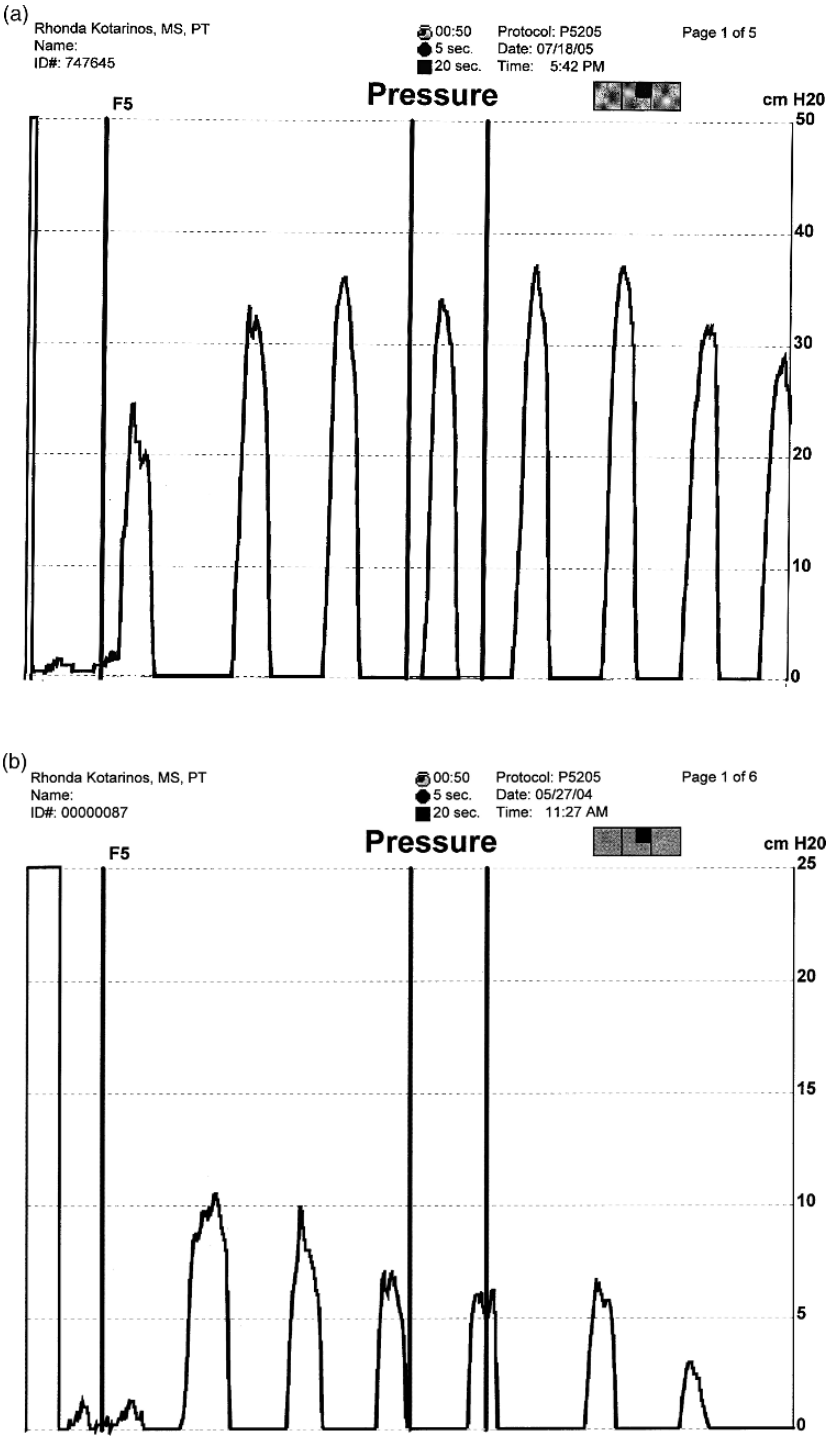

Fig. 1. Vaginal pressure profile during a pelvic floor shortening contraction. a) When the pelvic floor is of optimal length, there is a well-shaped curve with initial progressive increase in pressure before muscle fatigue results in decreasing pressure. b) When the pelvic floor is short, the first contraction is the maximal force with a declining force generation with subsequent shortening contractions.

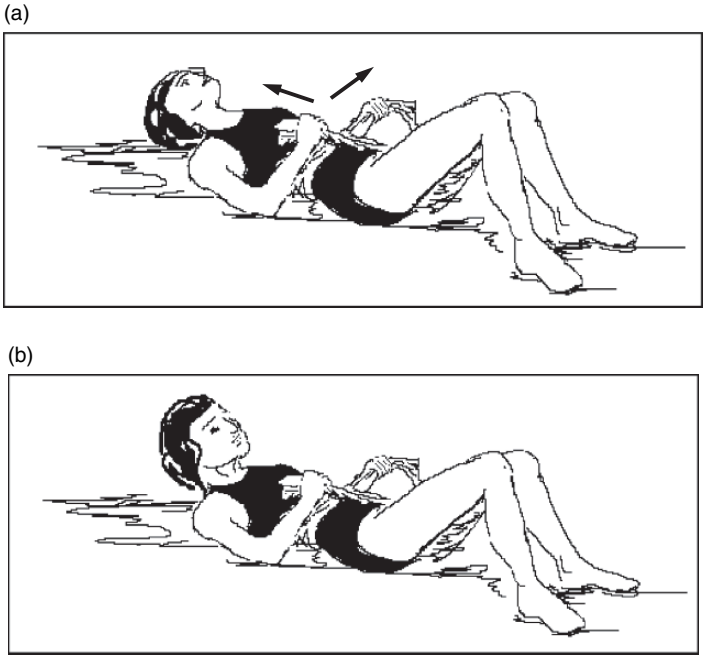

Fig. 2. Diastasis correction exercise. A sheet is used to correctly align the rectus abdominis muscles during neck flexion.

Connective tissue manipulation is utilized to treat the subcutaneous connective tissue restrictions. Subcutaneous panniculosis is another term to describe the connective tissue changes *(15)*. Release of the connective tissue restrictions through the use of manual manipulation reflexively facilitates the normalization of the pelvic floor musculature (Fig 3a–d). Myofascial trigger points associated with the referral zone frequently respond to the treatment of the subcutaneous panniculosis *(15)*.

All trigger points that relate to the pelvic floor directly or on a referral basis from other trunk or hip girdle muscles should be treated. There are multiple treatment options for directly managing trigger points. They include various manual release techniques, manual stretching with or without cold spray, myofascial release, muscle play, therapeutic stretching and dry needling or injections. As the trigger point resolves, an appropriate exercise program should be developed for the involved muscle.

Treatment of the short pelvic floor can begin during the evaluation. If the patient has no pelvic floor decent when asked to "drop their pelvic floor as if they were urinating," educating the patient at that time about a short pelvic floor is the beginning of treatment. Additionally, the clinician may find that the patient is a Valsalva voider if there is a strong bear down effort with their attempt to imitate voiding. If this occurs, it is important for the clinician to initiate the educational process to stop Valsalva voiding. Once the patient can successfully drop their pelvic floor, the patient will no longer have the need to Valsalva to initiate voiding.

Although assessing the shortening contraction, the clinician may ask the patient whether they perceive the post-shortening relaxation. If the patient can feel the post-shortening relaxation, they can be asked to release without contracting first. The verbal commands may need to vary. One patient may be able to perform the motion with the

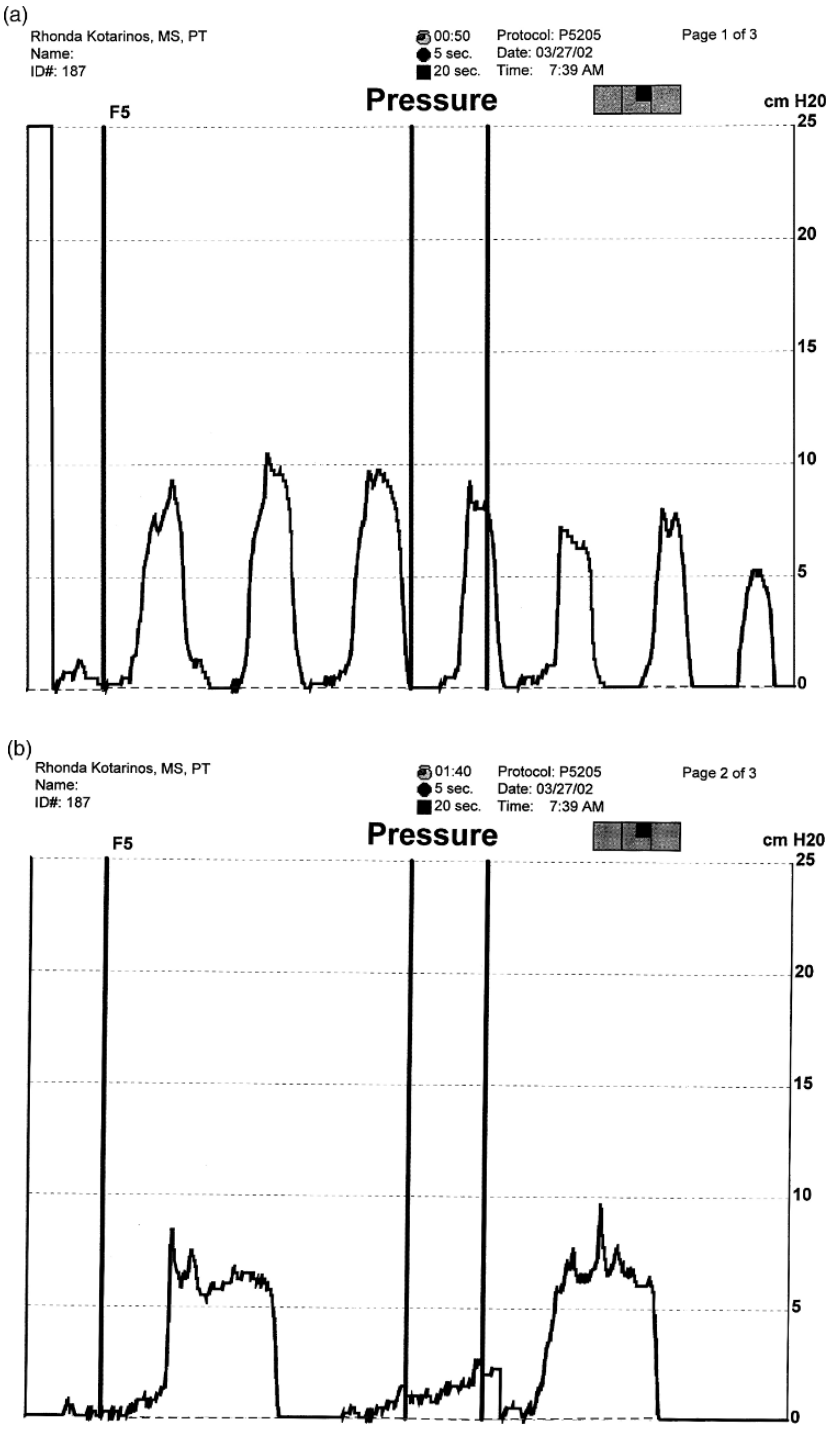

Fig. 3. Vaginal pressure profiles before and after connective tissue manipulation. a) Initial phasic shortening contraction. b) Initial endurance shortening contractions. c) Post-connective time manipulation phasic shortening contractions. d) Post-connective tissue manipulation endurance shortening contractions.

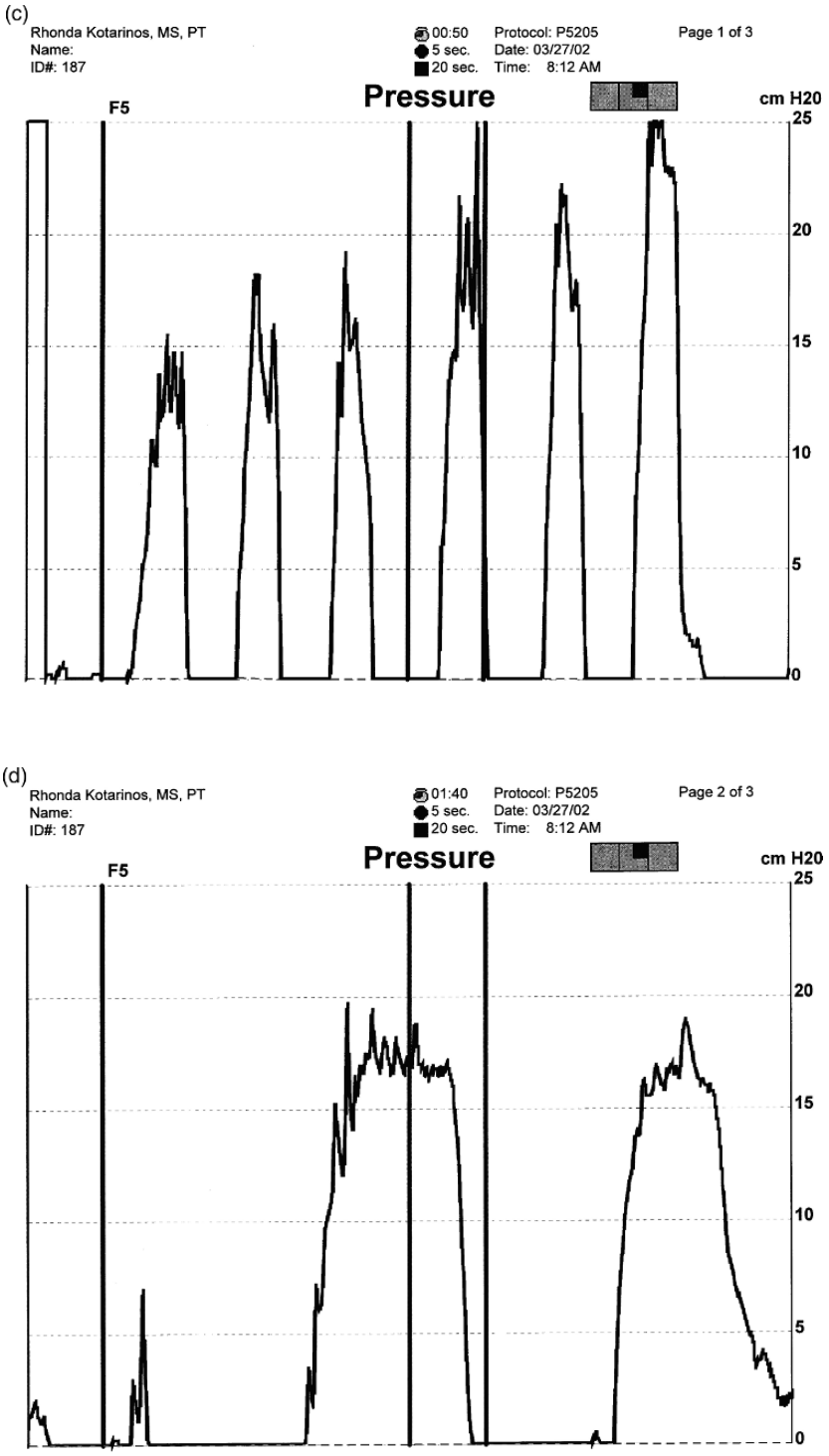

Fig. 3. (continued).

command of "drop" whereas another patient may perform better if the command is "let go, but do not squeeze first." On occasion, a passive stretch from a Valsalva maneuver or manually may be needed to expedite a lengthening contraction of the pelvic floor. During the performance of the Valsalva, the clinician may feel the initiation of the lengthening process which is quickly over ridden by the passive stretch of the bear down effort. In this case, the clinician could ask the patient to repeat the action but to not work as hard.

If all else fails, the clinician can turn to proprioceptive neuromuscular facilitation therapeutic exercise techniques. Proprioceptive neuromuscular facilitation is an exercise technique that utilizes the "less involved parts to promote a balanced antagonism of reflex activity of muscle groups and of components of motion" *(16)*. Pelvic floor function as it relates to micturition and defecation may be augmented by performance of related patterns of facilitation against maximal resistance. To inhibit the pelvic floor, resistance is applied by the patient to the bilateral symmetrical flexion, abduction, and internal rotation movement pattern of the hip. This is referred to as "knee pushes."

To execute this facilitation technique, the patient is in a supine position with the legs placed in a flexed, abducted, and slightly internally rotated position at the hip (Fig. 4a). With their hands placed on the anterior aspect of their thighs, the patient is asked to gently resist the flexion and abduction motion of their lower extremities (Fig. 4b). It must be stressed to the patient that the resistance should be very gentle.

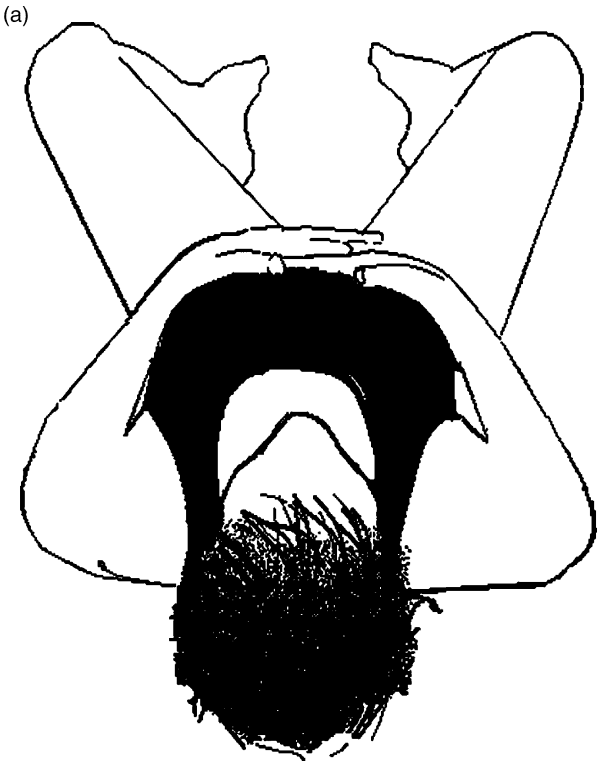

Fig. 4. Knee-push exercise to facilitate pelvic floor lengthening. a) Supine positioning with legs flexed abducted and slightly internally rotated at the hip. b) Hands placed on the anterior-lateral aspect of their thighs to resist flexion and abduction of the hips.

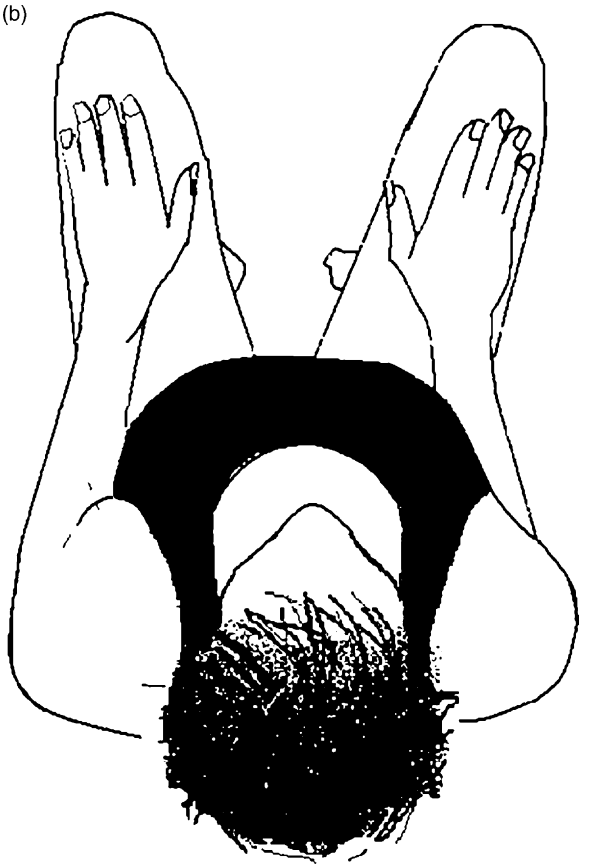

Fig. 4. (continued).

During trans-vaginal/rectal manual therapy, the clinician can provide a slight passive downward stretch to the pelvic floor during the maneuver. The action is repeated five times holding each for a 5-second hold. When the five repetitions are completed, the legs are returned to a hook-lying position and the patient is asked to drop their pelvic floor. For the home exercise program, the patient should repeat pelvic floor drops only if their proprioception is sufficient that they feel the lengthening of the pelvic floor and its return to the resting position.

The specific home exercise program for the short pelvic floor may initially be nothing more than to pay attention to what they do and feel when they initiate voiding. This is only appropriate if the patient is not a Valsalva voider. If the patient is not a Valsalva voider, the clinician would then add double voiding to the home program. This means that at the end of micturition, the patient should attempt to initiate voiding again. The assumption is that if they just dropped their pelvic floor to void, it should be easier to reproduce the motion at that time. It is stressed that the goal is not to get more urine out but to sense the descent motion of the pelvic floor. This can be repeated three to five times. Repetitions are minimal to reduce the risk of transitioning into a Valsalva maneuver. It may be necessary to suggest that the patient, male or female, should practice voiding in a full squat position. Males may need to minimize

their voiding in a standing position and use sitting or squatting to void until they have mastered the pelvic floor drop.

For their home program, knee pushes are performed in the morning at the start of their day and at night at bedtime. After their first void in the morning, the patient should do the knee push and drop routine so that they start their day with the pelvic floor in the longest resting position. At night, the patient should perform their usual personal hygiene routine and void just before getting into bed. Once in bed, the patient should do the knee push and drop routine just before they retire. When they perform a drop and have no sensory awareness of the drop, they should stop performing drops If they feel drop one, do two, but if they do not feel it they should not go on to the next repetition. Should the patient get up in the night to void the knee push and drop routine should be repeated after each void. Once the patient is able to drop with complete sensory awareness, they no longer need to perform knee pushes as part of their home exercise program.

Dropping of the pelvic floor is then incorporated into the management of their frequency and sense of urge. Lengthening of the pelvic floor is then used to eliminate inappropriate urges. Ideally, the patient would drop his or her pelvic floor five times for a 3- to 5-s hold and then become distracted with a very mentally challenging activity. As the pelvic floor assumes its more normal resting position, the patient will not getting inappropriate urge signals. The most significant comment from the patient is that they no longer even think about their bladder and that they went several hours before they even felt an urge.

NOTES

1. As they listen to the patient's description of their symptoms and the related history, the clinician should consider that there may be a short pelvic floor. Special note should be made if the patient has already had unsuccessful trials of physical therapy treatment that included traditional management.
2. During the transvaginal/rectal manual evaluation, the clinician should be assessing the quality and texture of the muscle tissue. The muscle may feel stiff and resistant to palpation, and the patient may complain of tenderness. Trigger points must be noted. Short pelvic floors do not necessarily have trigger points. The clinician must be careful not to describe this as a spasm. Very weak muscles have very poor tone.
3. Special attention should be given to the active shortening contraction. If one is extremely critical in their analysis of a short pelvic floor contraction compared with a very weak pelvic floor contraction, the nuances become evident. Usually, with a short pelvic floor there is adequate isolation, but there is a distinct compromise in the quality, range, and force.
4. The lengthening contraction may not be initially perceived by the clinician or the patient. The clinician may feel the return to the resting position and should confirm that this is not an active shortening contraction. After a lengthening contraction, the pelvic floor returns to its resting position passively.
5. Reevaluation of the pelvic floor motion can be done to provide the clinician and patient with objective feedback of the pelvic floor lengthening. After 3 to 5 lengthening contractions, a repeat shortening contraction is usually improved in its quality, force and range of motion. If this has occurred, the patient's proprioception is usually improved.
6. Instrumented evaluation with a pressure unit can be utilized, but should be considered a luxury. The skillful hands of a clinician are the most critical evaluation tool for a short pelvic floor.

7. When training the patient to drop their pelvic floor, the clinician must remember that there will be some abdominal muscle recruitment. The clinician has to monitor this abdominal activity visually, and manually through internal palpation, to insure that it does not exceed the normal reflex recruitment.

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21 Pharmacological Treatment of Pelvic Pain

Howard T. Sharp, MD

SUMMARY

The pharmacologic treatment of chronic pelvic pain requires knowledge about several classes of drugs. The standard approach is to use non-opioid drugs such as non-steroidal anti-inflammatory drugs or acetaminophen initially with or without non-opioid adjuvants (or adjuncts). Adjuvant therapy may include anticonvulsants, antidepressants, or a combination of both. Opioids are appropriate, safe, and effective in the treatment of non-cancer chronic pain. When initiating opioid therapy, patients should achieve a stable opioid dose with in a few months and thereafter be monitored regularly for pain relief, functionality, and side effects. Physicians who prescribe opioids should have an understanding of addiction, pseudoaddiction, tolerance, and dependence.

KEY WORDS: NSAIDs; narcotics; opioids; pelvic pain.

CONTENTS

INTRODUCTION

There are many pharmacologic pain-relieving agents designed to treat both general and specific targets within the human body, and no single class of therapeutic agents has been shown to be effective in treating all patients with a given pain state. Pain

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can be produced by different underlying mechanisms that may further complicate treatment. The ultimate goal is to achieve relief from pain and suffering. The goal of this chapter is to review several classes of drugs used to relieve pain. These will include non-opioid analgesics, analgesic adjuvants, and opioids.

NON-OPIOID ANALGESICS

This review of non-opioid analgesics will be limited to selected non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. Acetaminophen and NSAIDs are different from opioids in that they have a ceiling effect to analgesia, do not produce tolerance or physical or psychological dependence, and they work primarily by inhibiting the enzyme cyclooxygenase (cox; acetaminophen excluded) to prevent the formation of prostaglandins. These non-opioid analgesics are widely used in the United States, especially now that many are available as over-the-counter drugs including aspirin, ibuprofen, ketorolac, and naproxen sodium. In general, these are used for treating mild to moderate pain (Table 1).

NSAIDS

NSAIDs possess varying degrees of prostaglandin synthetase inhibition. Why is inhibition of prostaglandins important? Prostaglandins serve as mediators of inflammation and immune response modulation, renal function, platelet aggregation, differentiation of immune cells, wound healing, and nerve growth. When tissue is damaged, phospholipase A2 is activated, causing arachidonic acid to be cleaved from cell membrane phospholipids, to proceed down either the lipoxygenase pathway to form leukotrienes and lipoxins or the COX pathway to form thromboxanes and prostaglandins. Two isoforms of the enzyme COX have been demonstrated, COX-1 and COX-2. COX-1 is present in most tissues. It helps to maintain normal gastric mucosa and affects kidney and platelet function. Conversely, COX-2 is not present in most tissues but is inducible in peripheral tissues by pro-inflammatory cytokines

Table 1
Selected Oral Non-Opioid Analgesics Dosing

Drug	*Average analgesic dose (mg)*	*Dose interval (h)*	*Maximum daily dose*
Acetaminophen	500–1000	4–6	4000
Aspirin	500–1000	4–6	4000
Ibuprofen	200–400	4–6	2400
Naproxen	500	(Initial dose)	
	250	6–8	1250
Ketoprofen	25–50	4–8	300
Mefenamic acid	500	(Initial dose)	
	250	6	1500
Celecoxib	100–200	12	400
Ketorolac	10	4–6	40
	30[a]	6[a]	120[a]

[a]Parenteral route.

and produces prostaglandins that mediate inflammation and pain responses. In the stomach, COX-1 causes prostaglandin E-2 and prostaglandin I-2 to be produced, which are protective of the gastroduodenal mucosa. Therefore, when COX-1 enzymes are inhibited, gastric bleeding and ulceration can occur. COX-2 inhibitors are much more renal and gastrointestinal sparing.

The main disadvantages with the use of NSAIDs are gastrointestinal, renal, platelet, and hepatic toxicities, as well as anaphylaxis. Because NSAIDs inhibit prostaglandin synthetase in local tissues, patients with asthma, allergic rhinitis, and nasal polyposis are at an increased risk for anaphylaxis. Gastrointestinal toxicities are most common in patients with a history of peptic ulcer disease, concomitant glucocorticoid use, prolonged NSAID use, and age > 60. Based on data from the FDA, the risk of developing gastric ulcer with NSAIDs is between 2 and 4%. With COX-2 inhibitors, endoscopic data show the development of gastric ulcers to be similar to placebo. Patients with compromised renal function or those who use excessive doses are at risk for renal toxicity. Renal toxicity is usually in the form of interstitial nephritis, which manifests as nephritic syndrome. The effect of non-salicylate NSAIDs is reversible and related to the half-life of the drug; however, aspirin has an irreversible effect on platelets that lasts for the lifetime of the platelet. Therefore, patients undergoing surgery should abstain from aspirin use for at least 10 days.

In terms of efficacy, a Cochrane review of the use of NSAIDs to treat women with primary dysmenorrhea found them significantly more effective for pain relief than placebo (OR 7.91, 95% CI 5.65–11.09), although overall adverse effects were also significantly more common (OR 1.52, 95% CI 1.09–2.12) *(1)*. When NSAIDs were compared with each other, there was little evidence to suggest the superiority of any individual NSAID with regard to either efficacy or safety. The efficacy of NSAIDs in women with endometriosis is less clear, as a recent Cochrane review found inconclusive evidence for the use of NSAIDs in patients with endometriosis *(2)*.

Acetaminophen is a non-salicylate that has the advantage of having no antiplatelet effects and causing no damage to the gastric mucosa. Doses of up to 4000 mg daily are usually well tolerated; however, acute overdose can cause hepatic necrosis. Besides overdose, patients with liver disease or chronic alcoholism are at risk for hepatic necrosis. Acetaminophen has a potency similar to that of aspirin.

ANALGESIC ADJUNCT MEDICATIONS

Adjuncts to analgesics include anticonvulsants and various classes of antidepressant medications such as selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs). This group of adjunct medications is often used to treat neuropathic pain. Neuropathic pain has been defined by the International Association for the Study of Pain as pain resulting from disease or damage of the peripheral or central nervous system. It should be noted that this definition allows pain states without an identifiable primary lesion of the nervous system and allows a wide definition for the inclusion of complex regional pain syndrome I (CRPS I), previously reflex sympathetic dystrophy *(3)*. It is important to recognize neuropathic pain early as according to a survey performed by the American Pain Society, most people with chronic pain experience it for over 5 years before adequate treatment, with one-third of survey responders rating their pain as "the worst pain one can possible imagine *(4)*." It is estimated that over 4 million people in the United States suffer from neuropathic pain *(5)*.

Our current understanding of the use of these adjuvants in the treatment of neuropathic pain is based largely on studies conducted on patients with postherpetic neuralgia (PHN), diabetic peripheral neuropathy (DPN), and trigeminal neuralgia (TGN). Several randomized clinical trials (RCTs) have been performed in these patient populations and were reviewed by Backonja et al. *(6)*. Additionally, less well-studied pain syndromes such as central poststroke pain, spinal cord injury, and CRPS II have also yielded limited studies *(7)*. When considering the use of these drugs, it is useful to review both the number needed to treat (NNT) and the number needed to harm (NNH) to better understand efficacy and safety, respectively. To translate these concepts into clinical practice, the NNT is equal to the number of patients who would have to be treated to achieve a therapeutic response. This is calculated as the reciprocal of absolute risk reduction or difference between event rates in treatment and placebo groups or 1/(treatment response rate) – (placebo response rate). The NNH is the number of patients who would need to be treated in order for one to have an adverse event or 1/(treatment adverse event rate) – (placebo adverse event rate).

Anticonvulsants

In the 1940s, phenytoin and carbamazepine were used to treat the paroxysmal pain of TGN or "tic douloureux" or "epileptiform neuralgia." Paroxysmal pain may be associated with bursts of ectopic discharges from damaged nerves with excess voltage-sensitive sodium channels at end bulbs or at demyelinated areas of the affected nerve. Carbamazepine stabilizes membranes by inhibiting sodium channels. Although small trials have shown it to be effective in treating TGN, there are less data available about its use in the treatment of other neuropathies *(8)*. Likewise, phenytoin blocks sodium channels but is now considered to be second-line therapy. More recently, gabapentin, which binds to the neurotransmitter-gated calcium ion channels, has been shown to be effective in the treatment of neuropathic pain *(9)* in several RCTs involving the treatment of PHN *(10,11)* and DPN (Table 2) *(12,13)*. A single study has shown gabapentin to be effective in treating women with chronic pelvic pain *(14)*.

Gabapentin has gained popularity as a first-line agent in the treatment of neuropathic pain as it is usually better tolerated compared with most other anticonvulsants and TCAs in terms of side effects, without the toxicity of most anticonvulsants, obviating the need to obtain serum levels. It is absorbed by the small intestine and excreted in the urine. Doses needed to achieve success range from approximately 1800 to 3600 mg

Table 2
Gabapentin RCTs in the Treatment of Neuropathic Pain States

Reference	*Lesion*	*N*	*Dosing (mg)*
Rice *(10)*	PHN	334	1800–2400
Rowbotham *(11)*	PHN	229	1200–3200
Serpell *(9)*	ALL	307	1800–2400
Backonja *(12)*	DPN	165	1800–3200
Morello *(13)*	DPN	28	1565 (mean)
Gorson *(15)*[a]	DPN	40	900

ALL, combination of several neuropathies; DPN, diabetic peripheral neuropathy; PHN, postherpetic neuralgia.

[a]No statistically significant improvement in visual analog scores.

daily. Because it has a half-life of 6–8 h, it is best dosed three times daily. Doses of 900 mg daily have not been as effective as higher doses *(15)*. Dosing is usually started at 300 mg on day 1 and is increased by one tablet daily to achieve the intended dose. However, as with other adjuvant medications, some patients may not tolerate rapid dose escalation and will respond better to starting at 100 mg daily or t.i.d. It may be necessary to continue gabapentin at low doses for weeks until the patient becomes tolerant of the side effects. Furthermore, when gabapentin is discontinued, it should be tapered over 7 days.

The NNT for gabapentin has been reviewed for PHN and DPN as 3.2 (CI 2.4–5.0) and 2.8 (2.4–8.7), respectively *(16,17)*. The NNH was 2.5 (2.0–3.2) for DPN. A 2005 Cochrane review of 14 studies evaluating neurontin in chronic pain found evidence for its efficacy with an overall NNT of 4.3 (CI 3.5–5.7) and an NNH of 3.7 (CI 2.4–5.4) *(18)*. By way of comparison, the NNT for TCAs is 2.3 (1.7–3.3) for PHN and 3.0 (2.3–4.3) for DPN. The NNH for TCAs was 2.8 (2.0–4.7) for DPN.

The anticonvulsant pregabalin was granted final approval by the US Food and Drug Administration in 2005 after controlled substance scheduling (schedule V) by the US Drug Enforcement Agency. It is a structural congener of gabapentin, which binds to calcium channels to reduce neurotransmitter release, and has been shown to be effective in treating neuropathic pain *(19)*. It is usually started at doses of 25–50 mg t.i.d., up to 300 mg daily. The most common side effects are dizziness and somnolence. Another anticonvulsant drug, Lamotrigine may also provide benefit at a dose of 400–600 mg daily. It is usually started at 25 mg daily. It is metabolized by the liver and excreted by the kidney.

Tricyclic Antidepressants

Amitriptyline is the prototypical TCA used in the treatment of neuropathic pain. Other TCAs include Imipramine, Doxipin, Desipramine, and Nortyptaline. Amitriptyline is ideally dosed in the evening, starting at low doses of 10–25 mg due to anticholinergic side effects, coupled with the fact that it may be effective against neuropathic pain in doses less than typical antidepressant doses (150–300 mg). The onset of pain relief may come in two phases. There is often immediate pain relief reported as occurring within hours to days. Subsequently, a delayed onset of pain relief may occur 2–4 weeks later. TCAs have a much longer half-life when compared with the anticonvulsants, being around 20 h, allowing for once-daily dosing.

TCAs function by inhibition of the reuptake of serotonin and norepinephrine by the amine pump. RCTs have shown TCAs to be effective in the treatment of neuropathic pain (Table 3) *(20–22)*. A Cochrane review of antidepressants for neuropathic pain found antidepressants in general to be effective in alleviating pain, with the best

Table 3
Amitriptyline for the Treatment of postherpetic Neuralgia

Reference	*N*	*Dosing (mg)*	*Outcome*
Max *(22)*	58	12.5–150	Moderate relief
Watson *(20)*	35	100 (mean)	$p < 0.01$
Watson *(21)*	24	75 (mean)	$p < 0.0001$

Table 4
The Relative Side Effects Associated with Tricyclic Antidepressants

Drug	*Anticholinergic properties*	*Orthostatic hypotension*	*Sedation*
Amitriptyline	+++	++	+++
Imipramine	+++	+++	++
Clomipramine	++	++	++
Desipramine	+	+	+

evidence in favor of amitriptyline *(23)*. There were limited data for most SSRIs. When selecting a TCA, a few guidelines should be considered. First, potential cardiovascular side effects including aberrant cardiac conduction with prolonged QT interval, tachycardia, arrhythmias, and hypotension can occur with these medications. Therefore, these should be given to elderly patients with caution. Second, the degree of anticholinergic side effects should also be considered (Table 4). Desipramine has less anticholinergic side effects compared with amitriptyline as it does not inhibit norepinephrine uptake and may be a good option in patients complaining of excessive dry mouth or sleepiness.

SSRIs and SNRIs

The use of SSRIs and SNRIs for the treatment of neuropathic pain is a reasonable option for patients who do not tolerate TCAs or anticonvulsants. Paroxetine *(24)* and citalopram *(25)*, both SSRIs, as well as venlafaxine *(26)*, an SNRI, have been shown to be effective in the treatment of neuropathic pain.

Combination Pharmacotherapy

Although there are several drugs that have been shown to improve pain scores in studies, clinically, single-agent therapy can lead to incomplete efficacy with dose-limiting side effects. In such cases, combination pharmacotherapy may be used. Unfortunately, despite widespread use, there are few studies that have been published to help establish which combinations are additive, synergistic, or perhaps antagonistic. If combination pharmacotherapy is to be used, physicians should watch carefully for adverse events, especially in elderly patients. A treatment algorithm was proposed by Namaka et al., *(27)* suggesting that before combination pharmacotherapy or opioids are used, that patients should demonstrate failure with at least three different agents within the first-line drug classes (TCAs, anticonvulsants, and analgesics).

OPIOIDS

The term narcotic, though originally derived from the Greek word benumbing, has become more of a legal term with negative connotations. Because it describes some substances used for pain control that may not be derived from opium, the term opioid meaning opium-like is the preferred term. Opioids are extremely effective in the treatment of many pain states. Although opioids have typically been used for acute and chronic pain associated with cancer, the use of opioids for non-cancer pain is now an accepted practice also. In 1997, the American Academy of Pain Management and American Pain

Society published a consensus statement on the use of opioids for the treatment of chronic pain *(28)*. Furthermore, opioids were reviewed by way of a meta-analysis of 22 studies and were deemed to be effective in the intermediate-term treatment of neuropathic pain *(29)*. There continue to be barriers and misconceptions about long-term opioid use in patients with non-cancer chronic pain as some physicians are overly concerned that patients will become addicted and that they may be at risk of being disciplined by governmental agencies. This concern has lead to under-medication in many cases.

When considering the use of opioids for chronic pelvic pain, one should first obtain a comprehensive medical history and perform a physical examination. In keeping with the World Health Organization's pain relief ladder, developed for cancer pain relief, it should be established that conservative therapies have been tried adequately and have failed. The patient and physician should agree upon goals and have regularly scheduled follow-up visits to assess pain goals and evaluate for possible side effects. In general, the goals of opioid use in chronic pain are to reduce pain symptoms and to restore function. It should be understood that care must be individualized, as patients initiate therapy at different functional levels and progress at various rates. A patient–physician contract may be used to aid in the understanding that opioids will be obtained from a single source and that there are both risks and benefits to opioid therapy.

Available Opioids

Ideally, opioids are given orally when used in the outpatient setting. They may be administered by a number of other routes including parenteral, rectal, transdermal, transvaginal, and sublingual. Opioids are classified by the receptors to which they bind (mu, kappa, delta), the effect they produce such as agonist, partial agonist, antagonist, or mixed agonist/antagonist, and their duration of effect (short-acting or long-acting). Morphine is the prototypical opioid that is used for comparison with other opioids (Table 5). It is a short-acting, mu agonist, although it is now available in controlled-release preparations. Mu agonists are most widely used in opioid pain management as they have no analgesic ceiling effect. Partial agonists occupy part of an opioid receptor resulting in less analgesia when compared to a pure agonist. Mixed agonist/antagonist opioids are kappa opioid receptor agonists and either mu opioid receptor antagonists or neutral. Partial agonists (e.g., buprenorphine) and mixed agonist/antagonist opioids (e.g., butorphanol, nalbuphine, and pentazocine) have true dose ceilings and therefore should only be prescribed in doses approved by FDA labeling.

The use of long-acting opioids is helpful for patients who experience daily or mostly constant pain. Methadone is a good choice as it has a long half-life, or sustained-release

Table 5
Commonly Used Opioids with Equianalgesic Dosing

Drug	*Equianalgesic oral dose (mg)*	*Dosing interval (h)*	*Starting adult dose (mg)*
Morphine	30	4–6	15–30
Oxycodone	20	3–5	5
Codeine	130	4–6	30–60
Methadone	20	6–12	5–10
Hydromorphone	7.5	4	4–8

Table 6
Tramadol

Reference	*Lesion*	*N*	*Dosing (mg)*	*Outcome*
Boureau *(32)*	PHN	125	300–400	$p < 0.05$
Harati *(30)*	DPN	131	200–400	$p < 0.001$
Sindrup *(31)*	DPN	45	200–400	$p = 0.001$

DPN, diabetic peripheral neuropathy; PHN, postherpetic neuralgia.

formulations of morphine or oxycodone may be used. The initial dosing of a long-acting opioid is best accomplished by titration, based upon the amount of short-acting opioid used in a 48-h period. By determining an equipotent dose from short-acting opioid use, approximately 75% of the daily dose may be used with approximately 15% given in short-acting drug for rescue use. Typically, the long-acting opioid dose is adjusted over weeks (optimally within 2 months), decreasing the need for short-acting opioids. Once pain relief is established, the regimen is maintained, and the patient is continued to be seen regularly.

Tramadol

Tramadol has been shown to be effective in the treatment of chronic pain (Table 6), although the mode of action for this drug is not completely understood. Two complementary mechanisms are applicable: (1) binding of parent and M1 metabolite to opioid receptors and (2) weak inhibition of reuptake of norepinephrine and serotonin. Cases of abuse and dependence have been reported; therefore, the manufacturer recommends against its use in patients with known history of drug abuse. It has been shown to have an efficacy similar to that of TCAs or levorphanol in the treatment of DPN, PHN, and other polyneuropathy allodynia *(30–32)*. A 2004 Cochrane review found tramadol effective in the treatment of neuropathic pain with an NNT of 3.5 (CI 2.4–5.9) and an NNH of 7.7 (CI 4.6–20) *(33)*. The drug is well tolerated; however, approximately 20% suffer from nausea and constipation, and the incidence of somnolence and headache is 15%.

DOSE ESCALATION

The need for additional medication can be challenging to understand as it may reflect a number of causes including disease progression, increased activity, tolerance, opioid-induced abnormal pain sensitivity, addiction, or diversion. Therefore, an increased dosing requirement requires a re-evaluation of the patient. Addiction is a commonly misused term. It is usually associated with aberrant behavior including desperately seeking opioids despite adverse side effects. It is also called psychological dependence. Addiction and pseudoaddiction should not be confused. Some patients require additional dosing to achieve pain relief—the fear of pain may result in temporary desperate behavior that stops once relief is obtained. This phenomenon has been termed pseudoaddiction.

Dependence is a predictable, pharmacologic effect defined as a physiologic condition typified by an abstinence syndrome caused by abrupt discontinuation, significant dose

reduction, or administration of an antagonist. Opioid abstinence symptoms can range from mild (restlessness, anxiety) to severe (diarrhea, tachycardia, vomiting, abdominal cramping). Despite its sometimes dramatic appearance, the opioid withdrawal syndrome is rarely life-threatening or permanently disabling.

Tolerance in general is defined as the phenomenon in which an organism is less susceptible to the effect of a drug as a result of its prior administration. Acute tolerance is tolerance that develops rapidly following either a single dose or a few doses given over a short period of time, whereas chronic tolerance occurs when drug administration over a longer period of time produces reduced drug effects. For example, tolerance can develop with respect to respiratory and central nervous system function. This usually occurs within the first week of continuous opioid use. Tolerance to the analgesic and constipating effects of opioids does not occur in most patients once a stable dose has been established. Neither dependence nor tolerance is a predisposing factor for the development of addiction. However, some patients can develop opioid-induced abnormal pain sensitivity with the long-term use of opioids such that repeated administration of opioids not only results in desensitization, but can lead to a pro-nociceptive process of actual sensitization. Such patients are not good candidates for opioid use.

CONCLUSION

The World Health Organization's pain ladder, originally developed for pharmacologic guidance in cancer patients, is often extrapolated to be used in the non-cancer chronic pain patient. It is therein suggested that non-opioids with or without adjuncts be used as first-line therapy. If pain increases, weak opioids (e.g., codeine) with or without non-opioids and adjuvants may be used. Strong opioids with or without non-opioids or adjuncts are reserved for patients who do not respond to more conservative pharmacotherapy. It is important that patients be moved up the pain ladder appropriately to relieve suffering. Patients should be monitored for dose escalation and side effects by meeting with a medical care provider on a regular basis.

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22 Complementary Therapies for Genitourinary Pain

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Summary

Genitourinary (GU) pain is a complex subject with multiple possible causes and therapies. Chronic GU pain is often recalcitrant to standard treatment, and patients may be desperate to try anything in search of relief. Complementary and Alternative Medicine (CAM) has enjoyed increased popularity over the past decade, and many patients have sought pain relief from therapies such as herbs, acupuncture, and hypnotherapy. This chapter will review the topic of CAM and the state of the research in CAM therapies for GU pain.

Key Words: Genitourinary pain; complementary; alternative; integrative; mind-body; energy-based; herbs; supplements; acupuncture; CP/CPPS.

Contents

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TERMS AND DEFINITIONS

Many terms are used to describe CAM, each with slightly different connotations, but often used interchangeably. *Alternative Medicine* suggests that non-allopathic therapies will be used *instead of* allopathic therapies, and implies a tension between the two. *Complementary Medicine* considers the use of non-allopathic techniques in conjunction with *first line* allopathic approaches. *Holistic Medicine* suggests that mind, body, and spirit are intertwined, have an effect on each other, and must all be considered in healing and prevention of disease. Although this is a common theme of many "non-allopathic" therapies, there are many to which this term would not apply. *Integrative Medicine* implies that physicians will employ the *best* methods from a wide range of healing systems. "Best" implies an evidence-based decision that is also culturally and philosophically congruent with healer and patient.

In his landmark article, David Eisenberg defines CAM as interventions not taught widely in US medical schools or generally available in US hospitals *(1)*. This definition is rapidly becoming outdated. A survey of 125 US medical schools in 1998 (94% responding) found that 64% offered electives in CAM or included these topics in required courses *(2)*. This figure represents a doubling of earlier reported figures *(3)*. The National Center for Complementary and Alternative Medicine (NCCAM) at the NIH defines *Complementary and Alternative Medicine* as "a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine." NCCAM further states that while some scientific evidence exists regarding some CAM therapies, for most there are key questions that are yet to be answered through well-designed scientific studies—questions such as whether these therapies are safe and whether they work for the diseases or medical conditions for which they are used. The list of what is considered to be CAM changes continually, as those therapies that are proven to be safe and effective become adopted into conventional health care and as new approaches to health care emerge.

TRENDS

Before 1993, the best estimates of CAM usage in the American population was consistently around 5%. In 1993, Eisenberg reported that 34% of the US population had used one or more forms of CAM in the previous year, spending an estimated $13.7 billion. Visits to CAM practitioners outnumbered visits to all primary care providers that year *(1)*.

Dr. Eisenberg repeated this survey in 1997, revealing that the number of patients using CAM therapies increased to 42%, with an increase in the total visits from 427 million to 629 million (still outnumbering all PCP visits). The estimated spending increased to $27 billion. Unfortunately, patients are not any more comfortable disclosing their CAM use with their physicians in 1997 than they were in 1993. Seventy-eight percent reported not sharing this information with their physicians. An estimated 15 million people took herbs *with* their prescription medicine in 1997 *(4)*.

NATIONAL RESEARCH EFFORTS

The Office of Alternative Medicine at the National Institute of Health was established in 1992 with an initial budget of $2 million. The office began funding academic "Centers of Excellence" to research various CAM modalities and established a CAM

information clearing house. This office has enjoyed increased funding over the past years and was upgraded in 1998 to the National Center for Complementary and Alternative Medicine (NCCAM) with an annual operating budget of over $100 million. Within the NCCAM, there are several research centers with various emphases including addiction, women's health, cancer, AIDS, pediatrics, and pain. The NCCAM considers five major categories of CAM:

1. Mind–Body interventions
2. Manipulative and body-based methods
3. Alternative medical systems
4. Energy therapies
5. Biologically based therapies

Physicians need to maintain familiarity with the growing body of literature on modalities in each of the above categories. For instance, are there potential herb–drug interactions? Are patients likely to have benefit from their chosen therapy, or are they being "ripped off?" With the exploding body of evidence mounting with regard to CAM therapies, it is no longer appropriate for physicians to indicate that they "just don't have enough information." Furthermore, it is incumbent upon physicians to act as advocates for their patients by knowing the literature in this area and counseling their patients effectively.

As we explore the literature on CAM and genitourinary (GU) pain, it will be helpful to organize potential treatments into the above major categories.

MIND–BODY INTERVENTIONS

We are beginning to gain a deeper understanding of the influence that the mind and body have on each other. The study of psychoneuroimmunology has shown the importance of the interaction between mental and physical phenomenon. When either is out of balance, the other is also affected. For example, science has made us all aware of the physiologic ramifications of increased stress. The body produces "fight or flight" hormones such as cortisol, epinephrine, and norepinephrine to give us the temporary energy and strength we need in order to escape impending danger. A problem emerges when we are under chronic stress, as with busy two-income families, constant deadlines, and competition for limited resources. Our bodies, in this instance, produce chronically elevated levels of these "stress hormones." The result is immune system depression, cardiovascular compromise, and a host of other possible consequences. Mind–Body therapies are used to decrease stress and the levels of stress hormones in the body. Examples include relaxation therapy, music therapy, hypnosis, meditative exercises (yoga, tai chi, qi gong, and dance therapy), art therapy, prayer, support groups, and biofeedback.

Several studies have explored the role of biofeedback in men with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). It is hypothesized that pelvic floor tension is a contributing factor in CPPS. Biofeedback utilizes electrodes to transduce muscle potentials into auditory or visual signals, which enables patients to learn to voluntarily increase or decrease muscle activity of the pelvic floor. Insufficient relaxation of the pelvic floor results in hesitancy, intermittency, and high post void residuals *(5)*. In one small pilot study, 8 of 11 patients with CP/CPPS had significant improvement in either pain scores or chronic prostatitis pain index scores *(6)*.

In a larger study, 62 men with CPPS category III, having failed conventional treatments such as antibiotics and alpha-blockers for over 6 months, were treated with 20 minutes of biofeedback five times a week for 2 weeks. Sixty patients were significantly improved. Pain relief occurred after 2–3 treatments, and symptoms disappeared after 4–5 treatments *(7)*. In another, more recent study, 31 men with CPPS category III underwent 6–8 biofeedback treatments resulting in a decline of the mean total Chronic Prostatitis Symptom Index (NIH-CPSI) by 50%. In this study, a rectal EMG probe was used to measure resting tone of the pelvic floor muscles, and the mean value of the muscle tonus decreased from 4.9 at diagnosis to 1.7 after treatment *(8)*.

Biofeedback is a safe and effective treatment for refractory CP/CPPS. Larger trials with long-term follow up should be completed to determine the optimal number of treatments required to maintain lasting effects.

MANIPULATIVE AND BODY-BASED METHODS

Included in this category are massage therapy, spinal manipulation, Trager, Alexander, Feldenkrais, and Rolfing. The underlying premise is based on the belief that dysfunction of one part of the body affects the function of other discreet, non-connected body parts.

Spinal manipulation has been suggested as a possible approach to treatment of chronic pelvic pain, as well as primary and secondary dysmenorrhea in women. Pelvic organs are connected functionally through shared common nerve pathways. Bowel and bladder symptoms can accompany gynecologic symptoms, such as dysmenorrheal and vulvodynia. Osteopathic manipulative treatment (OMT) directed at stabilizing the pelvic bowl and/or the structures contained within it is used for the treatment of chronic pelvic pain *(9)*. One hypothesis is that mechanical dysfunction in vertebrae can lead to decreased spinal mobility, affecting the sympathetic nerve supply to the blood vessels supplying the pelvic viscera, resulting in vasoconstriction and dysmenorrhea. A recent Cochrane Database review found four trials of high velocity, low amplitude manipulation for dysmenorrhea, and found it to be no more effective than sham manipulation, though it was possibly more effective than no treatment *(10)*. This may simply highlight the difficulty in designing randomized, placebo-controlled trials using sham treatments in CAM therapies. More research is needed in this area.

Myofascial pain syndrome is common, and myofascial trigger point release is a manual therapy used in the treatment of this syndrome. A trigger point is defined as a hyperirritable, sensitive spot, usually within a taut band of skeletal muscle of fascia. Electrophysiological studies suggest active loci within dysfunctional extrafusal motor endplates. A study of 138 men with refractory CP/CPPS were treated for 1 month with myofascial trigger point release therapy, with significant improvement in pain and urinary symptoms scores *(11)*.

ALTERNATIVE MEDICAL SYSTEMS

Many persons employ traditional healing practices emanating from other cultures. Health is based on the principle of internal balance and harmony. When harmony and balance break down, there is disease. For most of these practices, scientific studies are not available.

Ayurveda is an ancient eastern Indian form of healing with roots in Hindu philosophy.

Traditional Asian Medicine has existed for at least 4000 years and consists of acupuncture, moxibustion, herbal medicine, cupping, therapeutic exercises, and dietary advice.

Other Native Healing Traditions include Native American Healing, Curanderos, Ispiritismos, and Traditional African Healing.

Homeopathy is based on the principle of treating "like with like." For example, a substance that causes symptoms of illness in a well person can also be used, in minute doses, to cure similar symptoms when they result from illness.

Acupuncture has become significantly westernized, and therefore is mentioned separately, although it is an integral part of Traditional Chinese Medicine. The exact mechanism of action is still unclear, but a growing body of evidence has shown acupuncture to be effective for a number of problems.

Multiple studies have looked at acupuncture for dysmenorrhea. One placebo-controlled trial of 57 women revealed a 93% success rate defined as resolution of dysmenorrhea, and no need for pain medications for 2 years following treatment *(12)*. Acupuncture point injection with Vitamin K3 is the standard treatment for severe dysmenorrhea in the Menstrual Disorder Clinic in Fudan University in Shanghai. A recent pilot study of 40 women in China and Italy showed immediate relief of acute menstrual pain, which extended through the non-treatment follow-up cycles after injection of Vitamin K into prescribed acupuncture points. Subjects reported fewer daily life restrictions, fewer hours in bed, fewer pain medications, and lower scores of menstrual pain and intensity *(13)*. There are fewer studies in secondary dysmenorrhea. A recent case report of two adolescents with endometriosis-related pelvic pain refractory to standard anti-endometriosis therapies showed modest improvement after 9 and 15 treatments over a 7- to 12-week week period. Improvements were also noted in headaches, nausea, and fatigue *(14)*.

Other studies have shown acupressure to have significant benefits in dysmenorrhea, enabling the woman to self-treat. One revealed the efficacy of acupressure to be equal to ibuprofen and significantly better than sham acupressure in 216 high school females *(15)*. A specific acupressure point above the ankle, known as the Sanyinjiao point, was shown to significantly reduce menstrual pain when stimulated for 20 minutes compared with 20 minutes of rest in a study of 69 college women *(16)*. Another study revealed the intensity of the dysmenorrhea remained significantly diminished 30 minutes after the 20-minute acupressure session in 58 college students *(17)*.

A study was undertaken to investigate the effects of acupuncture in low back and pelvic pain in women between their 15th and 30th week of pregnancy. Average pain scores decreased by at least 50% in 78% of patients treated with acupuncture combined with conventional therapy versus 15% of patients treated with conventional therapy (paracetamol 500 mg and hyoscine 10 mg) alone.

Acupuncture has also been studied in men with refractory CP/CPPS. In one small trial of 12 men undergoing a minimum of 6 weekly acupuncture treatments, a significant decrease occurred in total NIH-CPSI scores as well as NIH-CPSI pain, urinary, and quality of life scores after an average of 33 weeks of follow-up *(18)*. In another study of 10 men with CP/CPPS and intrapelvic venous congestion measured by transrectal ultrasonography and magnetic resonance venography, not only was pain and quality of life significantly improved on the NIH-CPSI, but the intrapelvic venous congestion significantly decreased compared with baseline *(19)*.

ENERGY THERAPIES

Therapeutic touch, healing touch, reiki, transcutaneous nerve stimulation (TENS), and magnet therapy are the most well-known forms of energy therapies. They are based on the concept that our bodies are all made of electromagnetic energy that can be influenced by another source of electromagnetic energy. No studies could be found on most forms of energy therapies, but magnet therapy has gained increased exposure in the literature recently.

There is evidence that CP/CPPS is a result of pelvic floor muscular dysfunction and/or neural hypersensitivity/inflammation. It has been hypothesized that the application of electromagnetic therapy may have a neuromodulating effect on the pelvic floor spasm and neural hypersensitivity. Two small studies have examined magnetic stimulation in men with CP/CPPS. In one, 21 men were randomized to receive either active electromagnetic or placebo therapy. The active therapy received 15 minutes of pelvic floor stimulation (in a special chair) at 10 Hz followed by 15 minutes at 50 Hz twice weekly for 4 weeks. Mean symptom scores decreased significantly in the actively treated group at 3 months and 1 year, compared with the placebo group, which showed no significant change *(20)*. In another trial, 14 men were treated with 30 minutes of sacral electromagnetic stimulation of 50 Hz once per week for 10 sessions. The mean total NIH-CPSI score did not change with treatment *(21)*.

Magnet therapy has been investigated in one small trial of 35 women with primary dysmenorrhea. Women were randomized to the use of either a static magnetic device (2700 gauss) or an identical, but weaker, magnetic placebo device (140 gauss), which were to be secured to the underwear anterior to the pubis. Women were asked to apply the device 2 days before the anticipated start of the next menstrual cycle and to leave the device in place except during bathing until the end of the cycle. The women in the active treatment group experienced a significant reduction in pain compared with the placebo group.

BIOLOGICALLY BASED THERAPIES

Herbs and supplements are the fastest growing market segments in pharmacies and mass-market retail outlets. They are no longer relegated to health food stores and mail-order houses. A recent study noted that herbal use was the CAM modality, which increased the most between 1990 and 1997 *(4)*. Approximately 30% of American adults reported using herbs and spending over $5 billion on them in 2000. Major health insurance companies are beginning to consider including herbs and supplements on their formularies. As herbs are becoming more an integral part of American culture, increased efforts will be required in evaluating the quality, safety, potential benefits, effectiveness, and appropriate therapeutic use of these products.

Although herbs and supplements exert pharmacological effects in vivo, under the current US regulatory framework they are considered foods, not drugs, and are therefore not regulated as stringently as drugs. Moreover, because these products are often not patentable, companies would never be able to recover the large costs of research required for FDA approval. Consequently, the 1994 Dietary Supplement Health and Education Act permits herbs to be sold as dietary supplements provided that therapeutic claims are not specified on their labels. Unlike drugs, the FDA must prove that a botanical is unsafe before it can be removed from the market. Merely proving it ineffective does not warrant removal.

A number of studies have looked at nutraceuticals for the treatment of primary dysmenorrhea. One mechanism underlying dysmenorrhea is the disturbed balance between anti-inflammatory, vasodilator eicosanoids derived from omega-3 fatty acids and pro-inflammatory, vasoconstrictor eicosanoids derived from omega-6 fatty acids. The high intake of omega-6 fatty acids in the western diet results in a predominance of omega-6 fatty acids in the cell wall phospholipid *(22)*. After the onset of progesterone withdrawal before menstruation, these omega-6 fatty acids, particularly arachadonic acid, are released, and a cascade of prostaglandins and leukotrienes produces both cramps and systemic symptoms such as nausea, vomiting, bloating, and headaches. Increased intake of omega-3 fatty acids can reverse the symptoms of dysmenorrhea by decreasing the amount of omega-6 fatty acids in cell membranes *(23)*. In a study of 42 adolescents with primary dysmenorrhea, girls were randomly assigned to either fish oil with vitamin E daily for 2 months followed by placebo daily for 2 months, or placebo followed by fish oil. There were no differences in the Cox Menstrual Symptom Scale between the two groups at baseline and after 2 months of placebo administration. After 2 months of treatment with fish oil, there was marked reduction in the Cox Menstrual Symptom Scale *(24)*. A more recent study compared Neptune Krill Oil (NKO) with omega-3 fatty acids in 70 women with primary dysmenorrhea. NKO is a natural health product extracted from Antarctic krill, a zooplankton crustacean rich in phospholipids and triglycerides carrying long-chain omega-3 fatty acids, as well as vitamins A and E. Women taking NKO 2 g/day during the first month of the trial, and two grams/day 8 days prior to, and two days during menstruation during the following 2 months of the trial, showed a significant improvement compared to baseline, as well as to the group taking fish oil in an identical manner *(25)*.

In a recent review of the diagnosis and management of dysmenorrhea, thiamine, pyridoxine, magnesium, and fish oil were all found to provide symptomatic relief in women with primary dysmenorrhea with few side effects. A low fat vegetarian diet showed significant reduction in symptoms in one small (randomized controlled trial RCT), and physical exercise reduced dysmenorrhea in several small studies *(26)*.

Pycnogenol, a standardized extract from the bark of the French maritime pine has been shown to possess anti-inflammatory actions. One study of 47 women with dysmenorrhea showed significant reductions in pain using Pycnogenol 30 mg orally twice daily over 3 cycles *(27)*. Pycnogenol 30 mg/day has also been shown to relieve back, hip, and pelvic pain in a group of 140 women in the third trimester of pregnancy *(28)*.

Rose tea has long been used in the folk treatment of dysmenorrhea in various regions of the world. In one recent RCT, 130 adolescents with primary dysmenorrhea were given either rose tea or no intervention for a total of six menstrual cycles. The treatment group perceived less menstrual pain, distress, and anxiety and showed greater psychophysiologic well-being compared with the control group. Rose tea is made from the rosebuds or rose leaves of *Rosa gallica*, which contains vitamins A, B, C, K, and P. The mechanisms behind rose tea's effectiveness for dysmenorrhea remain unclear.

The use of micronized flavonoids has recently been studied for abnormal uterine bleeding and the dysmenorrhea associated with it. These flavonoids have been shown to suppress prostaglandins E2, F2alpha, thromboxane A2, and prostacycline; reduce capillary fragility; and increase lymphatic drainage. In 36 patients with abnormal uterine bleeding and dysmenorrhea treated with 1 g/day of micronized flavonoids 5 days before the expected onset of menstruation, and up to the end of bleeding for three consecutive

cycles, menstrual bleeding was significantly decreased, and there was noted to be a 50% improvement in associated dysmenorrhea in 75% of the subjects *(29)*.

Intakes of soy, fat, and dietary fiber may be associated with symptoms of dysmenorrhea through their biological effects on estrogens or prostaglandin production. A study of 276 Japanese females was conducted using a validated semiquantitative food frequency questionnaire. Severity of menstrual pain was assessed by the multidimensional scoring system reported by Andersch and Milson. Intake of dietary fiber was significantly inversely correlated with the menstrual pain scale. Neither soy nor fat intake (total, saturated, monounsaturated, or polyunsaturated fat) was significantly correlated with menstrual pain *(30)*.

Nutraceuticals have also been studied but to a much lesser extent for CP/CPPS. Saw palmetto, pollen extract, and quercetin have data specific to CP/CPPP.

Saw palmetto is commonly used in the treatment of benign prostatic hypertrophy. Studies have suggested properties and efficacy similar to that of finasteride. In a prospective, open-label 1 year trial of 64 men with CP/CPPS randomized to either finasteride or saw palmetto, the men in the finasteride group had significant reductions in the NIH-CPSI score, compared with no symptom reduction in the saw palmetto group *(31)*. Another study tested a standardized extract of saw palmetto called Permixon in 61 men with category 3B prostatitis and found 65% of the Permixon group reported improvement on the Patients Subjective Global Assessment.

A specific pollen extract called cernilton has been used for a variety of urologic conditions and has been shown in clinical studies to give marked symptom reduction in men with CP/CPPS *(32)*. A recent RCT using a standardized extract called Prostat/Poltit in 60 men with CP/CPPS for 6 months. The patients receiving Prostat/Poltit had a significantly lower pain score, less voiding symptoms, and less storage symptoms at the end of the 6-month period. No adverse effects were reported *(32)*.

Quercetin belongs to a group of polyphenolic substances known as flavonoids. It is commonly found in onions, grapes, and green tea, and is often used for its antioxidant/anti-inflammatory effects. One RCT tested quercetin in men with CP/CPPS for 1 month, revealing significant improvement in the NIH-CPSI score compared with placebo *(33)*.

SUMMARY

GU pain can have devastating effects among individuals chronically suffering from it. Many complementary therapies have been studied for their use in GU pain and may be invaluable as adjunctive or even first line therapy for this chronic condition. Biofeedback, acupuncture, acupressure, omega-3 fatty acid supplementation, increased dietary fiber, and myofascial trigger point release are all inexpensive, readily available therapies that may have an immense impact on patients with GU pain. Other therapies, such as pelvic electromagnetic therapy, pollen extract, saw palmetto, rose tea, and pycnogenol may be promising additions to our armamentarium, and certainly warrant further study in this area.

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V Iatrogenic Causes of GU Pain or Inflammation

23 Rectourethral Fistulae

Brian R. Lane, MD
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Summary

Etiologies of rectourethral fistula (RUF) include trauma, inflammatory processes, congenital defects, and prior pelvic surgery. Increasingly, RUF is being diagnosed in men who have received radiation therapy for prostate cancer. The most common presenting symptoms of RUF include passage of urine per rectum, irritative voiding symptoms, pneumaturia, and fecaluria. Spontaneous closure of RUF is uncommon and has not been reported in patients with RUF caused by radiation toxicity. Selection of an appropriate surgical approach is dictated by the clinical situation, life expectancy, pre-treatment urinary and bowel function, and local adjacent tissue damage. This chapter focuses on the diagnosis and surgical management of patients with iatrogenic and radiotherapy-induced RUF.

Key Words: Rectourethral fistula (RUF); radiation toxicity; prostate cancer; surgery; York-Mason repair.

Contents

INTRODUCTION

The historic etiologies of rectourethral fistula (RUF) include trauma, inflammatory processes, congenital defects, and prior pelvic surgery *(1)*. A number of patients continue to present with RUF due to these causes, but we have also noted a recent

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increase in the number of men presenting with RUF following radiation therapy for prostate cancer *(2)*. Of the 315 cases of RUF reported through 1997, only 12 cases (3.8%) involved patients who received radiation to the pelvis *(1,3–6)*. Since 1998, 113 of the 228 reported cases (49.6%) occurred in patients with exposure to pelvic radiation *(2,7–19)*. We believe that the increased number of cases of radiotherapy-induced RUF is most likely because of the increased usage of brachytherapy (BT) and combined BT and external beam radiation therapy (EBRT) for the treatment of prostate cancer.

Spontaneous closure of RUF in general is uncommon and has not been reported for those caused by radiation toxicity *(7)*. Conservative surgical repair and reconstruction is often successful in the absence of pelvic radiation, but the tissue damage that accompanies most radiotherapy-induced RUF frequently leads to failure when these approaches are used. In these cases, fistula repair with interposition of healthy, well-vascularized tissue is a necessity. Selection of an appropriate surgical approach in the patient with a RUF is dictated by the clinical situation, life expectancy, pre-treatment urinary and bowel function, and local adjacent tissue damage. This chapter will focus on the diagnosis and management of patients with iatrogenic and radiotherapy-induced RUF.

DIAGNOSIS

The diagnosis of RUF is made primarily on the basis of the clinical presentation, with confirmation using voiding cystourethrography, cystoscopy, proctoscopy, and digital examination under anesthesia. The most common presenting symptoms include passage of urine per rectum, irritative voiding symptoms (71–93%), pneumaturia (50–85%), and fecaluria (21–68%) *(20)*. Hematuria, pelvic pain, hematochezia, and fever are additional symptoms that may be present. In our experience, rectal and pelvic pain associated with radiotherapy-induced RUF may be quite severe and debilitiating. Other potential major complications include life-threatening bleeding, intra-abdominal abscess, sepsis, and necrotizing fasciitis *(2)*. Iatrogenic RUF can present any time after surgery and between 6 months and 20 years after radiation treatment.

PRE-SURGICAL EVALUATION

No single treatment is ideal for every patient with a RUF. Proper management of each patient relies on five key factors:

1. *Sphincteric function*. Preservation of anorectal function using complex anal sphincter-sparing surgery should generally not be attempted in a patient with poor anal sphincteric pressure and function. End colostomy may represent optimal bowel management in this setting. Patients with an incompetent urinary sphincter may be candidates for urinary tract reconstruction if they are perceived to have adequate bladder function, as an artificial urinary sphincter can be placed after fistula repair in most cases. In the setting of a contracted and poorly compliant bladder, supravesical urinary diversion may be the best long-term solution.
2. *Presence of urethral stricture or bladder neck contracture*. Urethral stricture disease is not uncommon in patients with iatrogenic RUF. Obstruction distal to the fistula will compromise a technically adequate repair and should be treated beforehand or in some cases at the time of fistula repair.

3. *Status of adjacent tissue*. Radiation to the pelvis can cause damage to endothelial cells, connective tissue, and blood vessels *(21)*. As a result, radiotherapy-induced RUF are often large and can be associated with extended radiation field effects on the bladder and rectum as well as decreased vascularity, fibrosis, and at times necrosis of adjacent soft tissues. These RUF therefore require more extensive repairs with interposition of healthy, well-vascularized tissue, have higher failure rates, and occasionally require permanent fecal and/or urinary diversion.
4. *Size and location of fistula*. Small, distal fistulas in the absence of radiotherapy can often be repaired through a transanal or transsphincteric approach. Larger fistulas and those associated with radiation usually require a transperineal, abdominal, or combined approach with tissue interposition.
5. *Overall condition and life expectancy of the patient*. Poor surgical candidates may be best suited in certain instances for permanent fecal and/or urinary diversion.

Among imaging studies, preoperative antegrade and retrograde imaging of the lower urinary tract with a suprapubic catheter already in place provides the most useful treatment-planning information (Fig. 1). For RUF in which a major repair is anticipated, such as radiotherapy-induced RUF, cystoscopy, proctoscopy, and bimanual examination under anesthesia are performed in order to define the extent of the radiation damage and to generate a surgical plan *(2)*. Our experience is that urodynamics can be somewhat difficult to reliably perform in patients with a radiotherapy-induced RUF because of the occasional inability of patients to accumulate fluid in the bladder because of a large fistula, as well as poor patient tolerance related to discomfort. In this patient group, we have therefore relied primarily on the capacity and visual assessment of the bladder at the time of cystoscopy to determine suitability for functional preservation. Anal manometry is used selectively to aid in determination of rectal sphincter competence when equivocal.

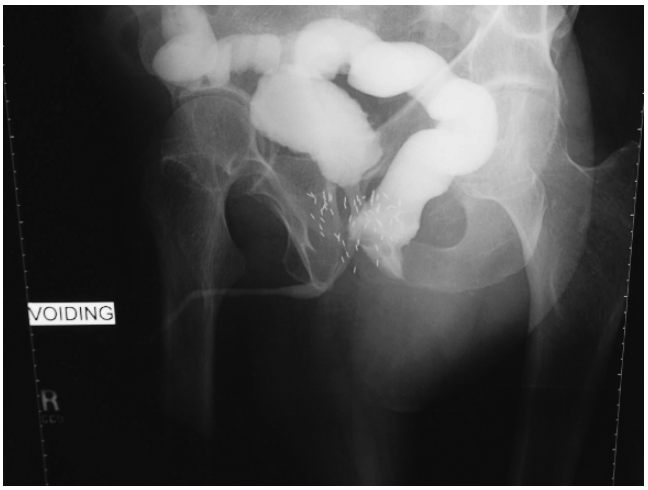


Fig. 1. Voiding cystourethrogram demonstrating large radiotherapy induced RUF.

SURGICAL MANAGEMENT

Diversion

The ultimate goal of treatment for RUF would be closure of the fistula with restoration of bowel and bladder function. Spontaneous closure has been reported in up to 25% of iatrogenic RUF *(22)*, but our previous experience, and that of others, has indicated that those caused by radiation toxicity do not heal spontaneously *(2,7,14)*. If a patient presents with a stable post-surgical RUF without evidence of surrounding inflammation or sepsis, fecal and urinary diversion are not always essential before repair and may be done at the time of surgery. However, it is probably never wrong to divert the fecal and urinary stream first to see whether fistula resolution will occur and to gain control of the situation. Conversely, if a patient with a radiotherapy-induced RUF has not already been diverted before referral, we believe that all patients should undergo fecal and urinary diversion soon after presentation in order to prevent sepsis and reduce inflammation in the area of the fistula. It should be noted that the chance of life-threatening bleeding or sepsis is very real in these patients *(2)*. Previous authors have almost unanimously supported initial fecal and urinary diversion in these patients as well, although one group has recommended diversion before surgical repair only in septic patients with diversion at the time of definitive surgery in all others *(7)*. We place a diverting ileostomy or colostomy and a suprapubic tube at the same time as diagnostic cystoscopy and proctoscopy. In the setting of obvious severe injury to the rectal sphincter, an end colostomy is generally used, as it would be anticipated to be permanent. If a reconstructive procedure is a potential surgical option, an ileostomy is preferred. Definitive surgery is anticipated 3–6 months after initial fecal and urinary diversion.

In some patients, initial urinary diversion with a suprapubic catheter and some form of fecal diversion may turn out to be the preferred long-term approach. Poor surgical candidates with large radiation-induced RUF are the patients most likely to be managed in this fashion *(2)*. In a small number of patients, permanent urinary and fecal diversion with pelvic exenteration may be indicated when pelvic sepsis and bleeding persist despite initial diversion and management.

Transanal Repair

The transanal approach with rectal advancement flap (Fig. 2) has been proposed for surgical treatment of RUF *(7,15, 23–26)*. For small non-radiated fistulas, this procedure is very well tolerated and represents the most minimally invasive form of surgical management. Reported success rates range from 75 to 100% *(7, 23–26)*. Unfortunately, radiotherapy-induced RUF have a higher recurrence rate with this approach, which is thought to be related to decreased local tissue vascularity and a lack of sufficient tissue interposition *(2)*. Transanal repair is our favored approach in selected patients with small non-radiated fistulas in an accessible area of the rectum, given the noted success rates and minimal postoperative morbidity.

York-Mason Repair

Popularized by Kilpatrick and York-Mason in 1969 *(27)*, the posterior transanosphincteric approach has been the most widely used technique for the repair of RUF (Fig. 3). With the patient in the prone jack-knife position, an incision is made in

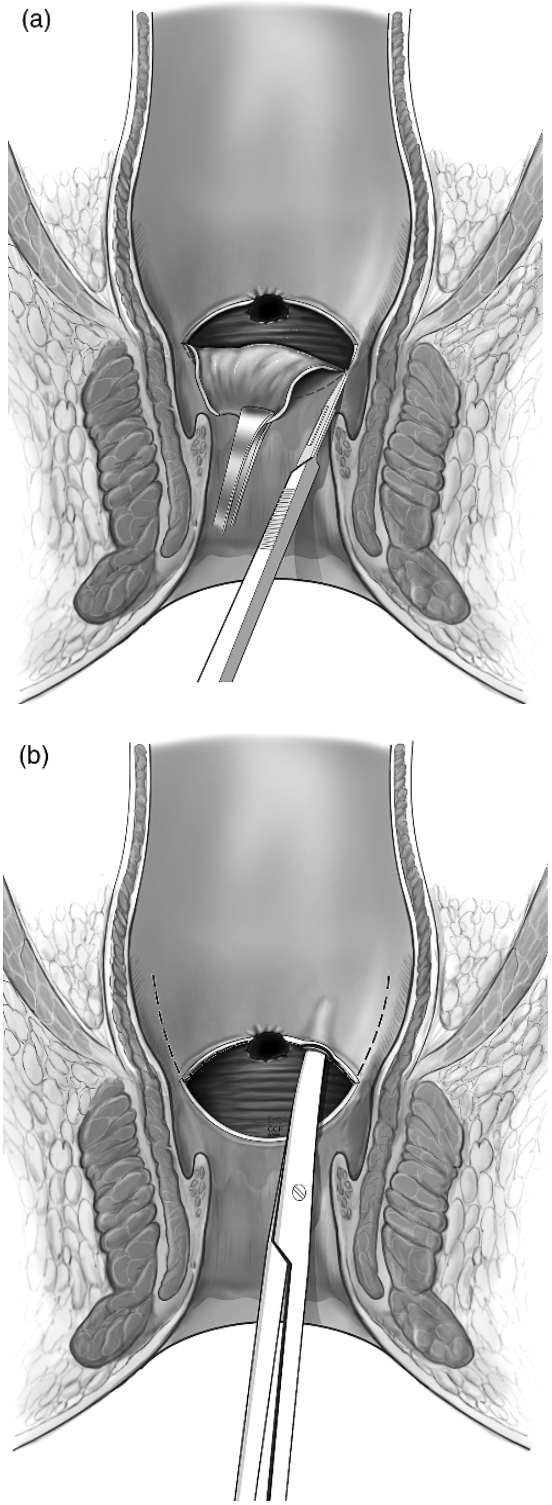


Fig. 2. Transanal repair of RUF: (a) Initial incision, (b) Mobilization of superior rectal flap, (c) Flap raised prior to fistula closure, (d) Rectal flap advanced and sutured.

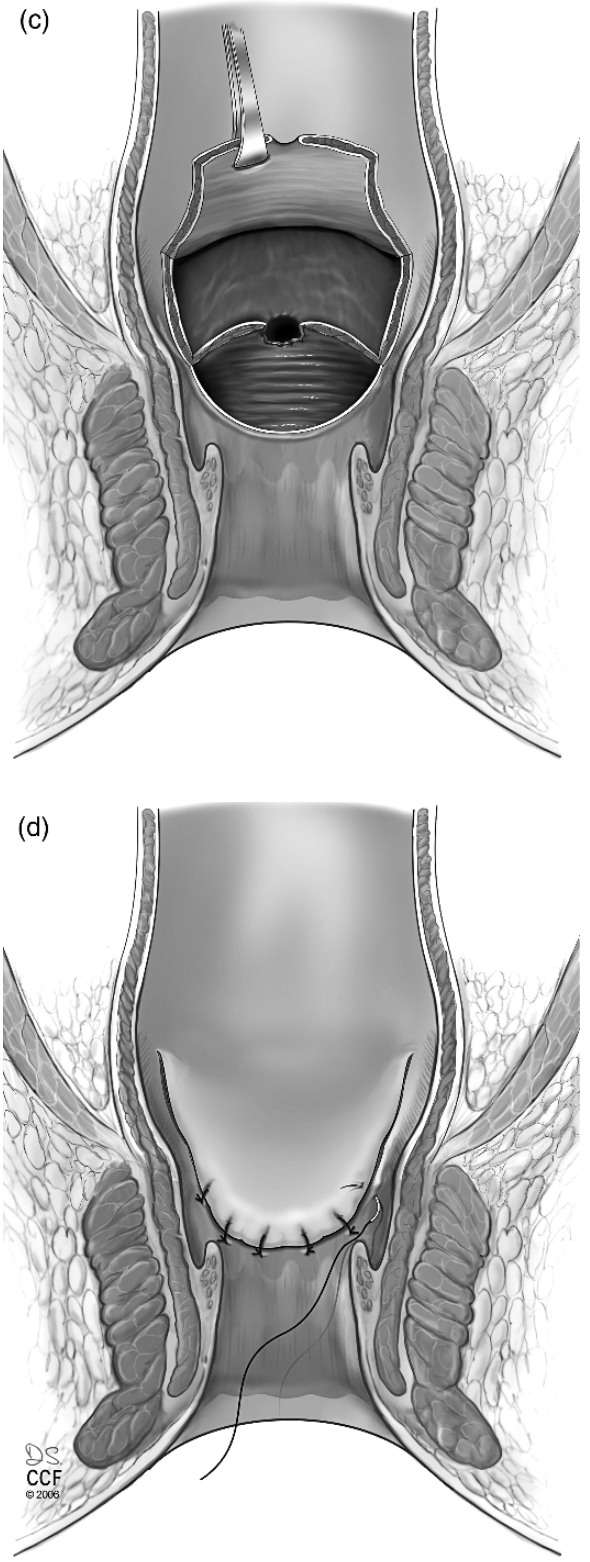


Fig. 2. *(Continued)*

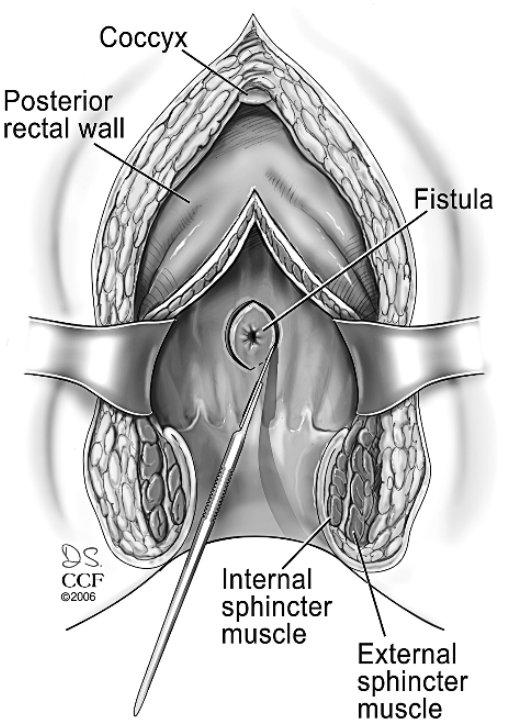


Fig. 3. York-Mason approach for repair of RUF.

the midline from the tip of the coccyx to the anal verge. The anal sphincter is divided with each component being labeled with sutures to allow for proper realignment at closure. The rectal mucosa is then opened along the entire length of the incision providing excellent exposure to the fistula. The fistula tract is sharply excised and a plane is dissected between the rectal wall and the urinary tract. The urethra and rectum are closed in layers, followed by closure of the rectal mucosa and anal sphincter. Alternately, a rectal flap repair as described by Parks may be performed through this exposure as well *(23,28)*. Although not reported universally, we have preferred to perform fecal and urinary diversion at the time of repair if not done previously. We feel that the York-Mason repair is most useful for small post-surgical fistulas that are too proximal for transanal repair. Patients with pre-existing anorectal dysfunction or potential for impaired wound healing because of radiotherapy or other diseases are best suited for an alternative approach. Excellent outcomes following York-Mason repair in properly selected patients have been reported without significant bowel dysfunction or fecal incontinence *(1,29)*.

Surgical Reconstruction for Large or Complex Fistulas—Preservation of Urinary or Bowel Function

Based on the pre-surgical evaluation, some patients with RUF are candidates for surgical restoration of only one system. The typical setting would be a patient with anorectal dysfunction or sphincteric incompetence who is a candidate for permanent colostomy and urinary tract reconstruction. Urinary reconstruction is optimized by

concomitant proctectomy, which can be difficult at times in the setting of previous radiotherapy. A small urethral fistula may be closed primarily, followed by omental mobilization to the pelvis for coverage of the area. Some fistulas too large for primary closure have been managed with omental or gracilis transposition alone *(3,30)*; however, we have preferred to close the urethral defect with a buccal mucosa graft in this setting as this seems to lead to decreased urinary extravasation and more rapid healing overall *(2)*. The buccal graft is buttressed with omentum or a gracilis muscle flap for optimal take (Fig. 4 and Color Plate 29, following p. 132).

Less commonly, the lower urinary tract may not be suitable for reconstruction because of a poorly compliant or contracted bladder. If the rectal sphincter is intact, cystectomy with ileal conduit urinary diversion and primary repair of the rectum may be performed with omental coverage *(2)*. If the rectum is extensively diseased, consideration can also be given to proctectomy with staged Turnbull-Cutait colo-anal pull through as an alternative if the sphincter is intact *(31)*.

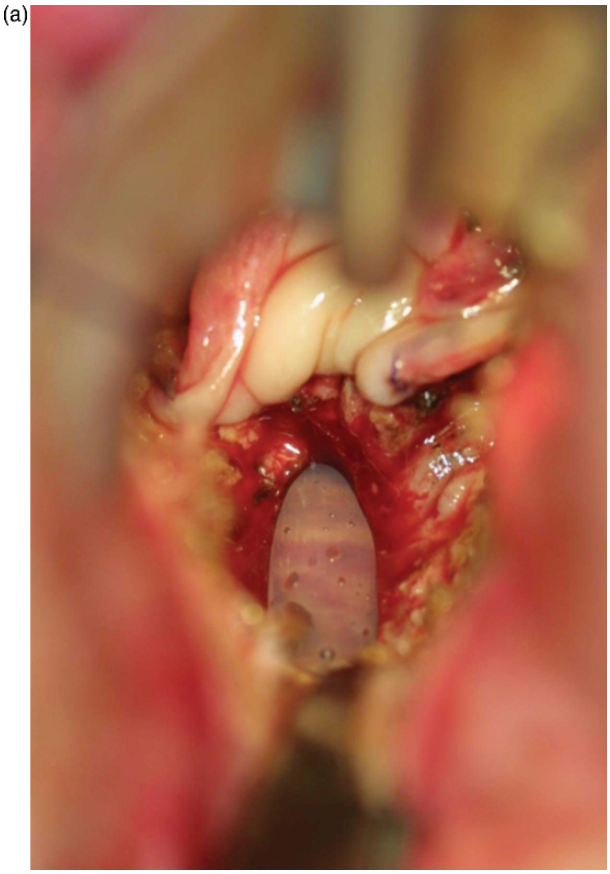
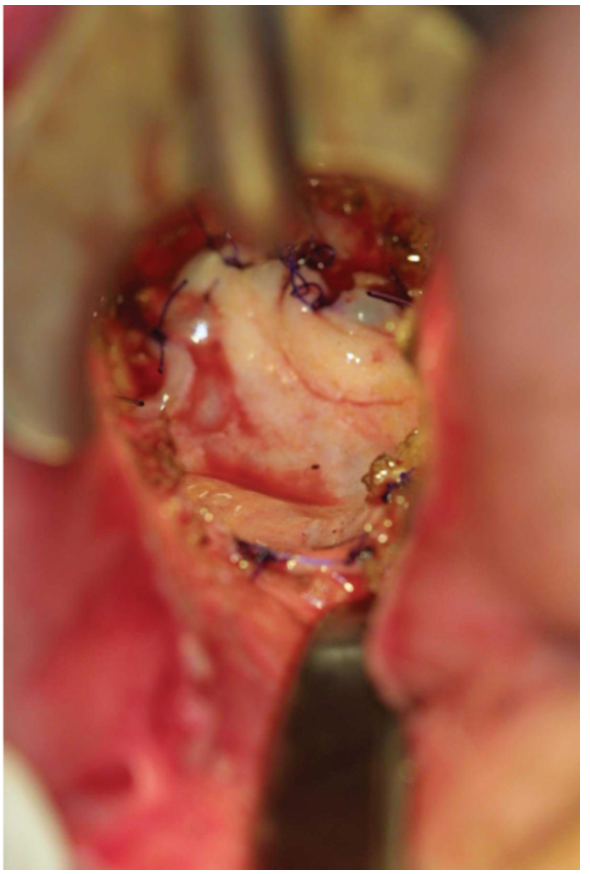


Fig. 4. Closure of RUF in the prone position using a buccal mucosa onlay graft: (a) Catheter visualized in urethral defect; (b) Buccal mucosa closure of defect; (c) Graft coverage with omental flap. (*see* Color Plate 29, following p. 132)

(b)



(c)

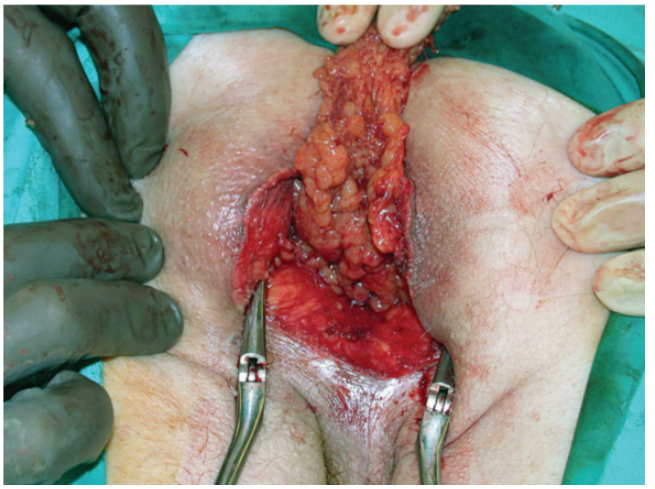


Fig. 4. *(continued)*

Surgical Reconstruction for Large or Complex Fistulas—Preservation of Urinary and Bowel Function

Transperineal Repair

Optimal surgical repair of a large or complex RUF involves interposition of healthy tissue, such as the omentum or gracilis muscle, into the plane between the rectum and the urethra *(7,14)*. The transperineal approach begins with very careful and meticulous dissection in the plane between the rectum and the prostate and bladder to the level of the peritoneal reflection. The plane of dissection typically starts superior to the anal sphincter and then is carried down onto the rectum, although an anterior transanosphincteric approach can also be performed in select cases *(17,32)*. When performing this maneuver, the musculature of the anal sphincter is tagged with sutures for later closure as described for a York-Mason repair. Development of the space between the urinary tract and the rectum can be quite difficult, as it is often performed in the setting of radiotherapy or previous attempts at fistula repair. Once completed, the urinary tract defect is closed primarily when feasible or patched with a buccal mucosa onlay graft. In the setting of an associated membranous urethral stricture, a urethrotomy incision is created from the level of the fistula through the stricture into the proximal bulbous urethra. Buccal mucosa is then grafted into the resulting urethrotomy defect, with distal graft coverage using the corpus spongiosum and proximal buttressing with a gracilis muscle flap *(17)*. The rectum is closed and the gracilis muscle is rotated into the space between the rectum and the urinary tract and anchored to the peritoneal reflection using interrupted sutures (Fig. 5 and Color Plate 30, following p. 132). Lateral sutures are also placed between the gracilis and the levators to insure that its position is maintained with complete coverage of the reconstruction. Primary closure of the urethral and rectal defects with gracilis interposition was successful in a combined 13 of 15 (87%) patients in two studies *(7,14)*. Zinman and colleagues have recently reported excellent results using a transperineal approach for repair of complex RUF with BMG closure of the urethra, primary closure of the rectum, and gracilis interposition *(17)*. We have used this technique in 8 patients to date with only one failure thus far, and will continue to use it in selected patients. It would seem to be most useful when the rectum and perirectal tissues are preserved well enough to allow adequate healing with primary rectal closure, as opposed to situations requiring resection of a severely diseased rectum and pull through of healthy colon.

Abdominoperineal Repair

We have successfully used an abdominoperineal approach in 5 patients in whom the rectum was deemed to be too extensively damaged by radiotherapy to allow a reliable primary closure because of either severe proctitis or extensive tissue loss *(2)*. In these cases, proctectomy and buccal graft closure of the urethral defect were done initially in the prone jack-knife position, and the patient was then placed supine for the remainder of the procedure. Turnbull-Cutait-staged colo-anal pull through is then carried out using an abdominal approach. We have found that simple rotation of the sigmoid mesentery anteriorly during the pull through provides an excellent host bed for the buccal mucosa graft when omentum is not available, or if there is insufficient room in the pelvis to accommodate the omentum. This approach achieves the goals of management of RUF caused by severe radiation injury; it enables repair of large fistulas, restores fecal and urinary continuity, and eliminates a severely diseased rectum. Potentially difficult

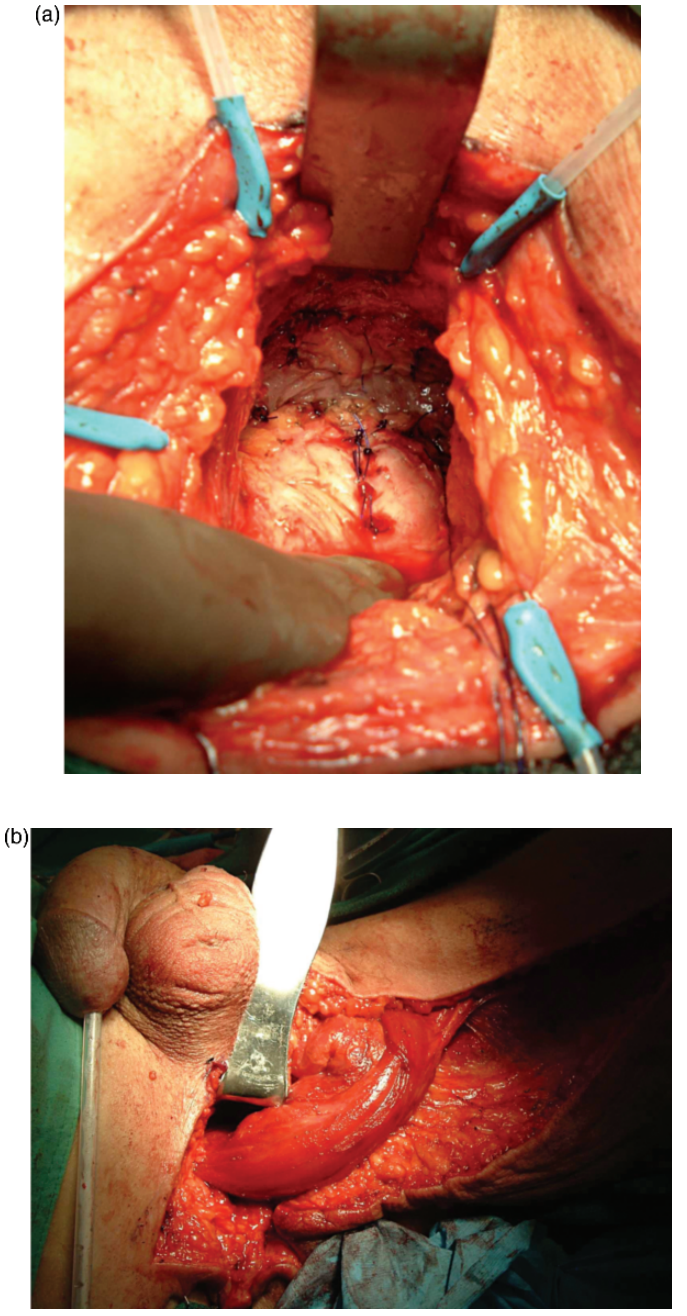


Fig. 5. Transperineal closure of radiotherapy induced RUF: (a) Dissection to the level of the peritoneal reflection with primary closure of rectum (R) and buccal graft closure of prostatic urethral defect (*); (b) Gracilis muscle interposition. (*see* Color Plate 30, following p. 132)

aspects of this procedure include the morbidity of an abdominal operation and the need to reposition the patient from the prone to the supine position during the case. A minor potential complication that we have encountered in 2 patients is the occurrence of minor rectal ectropion that may require simple outpatient excision at a later date.

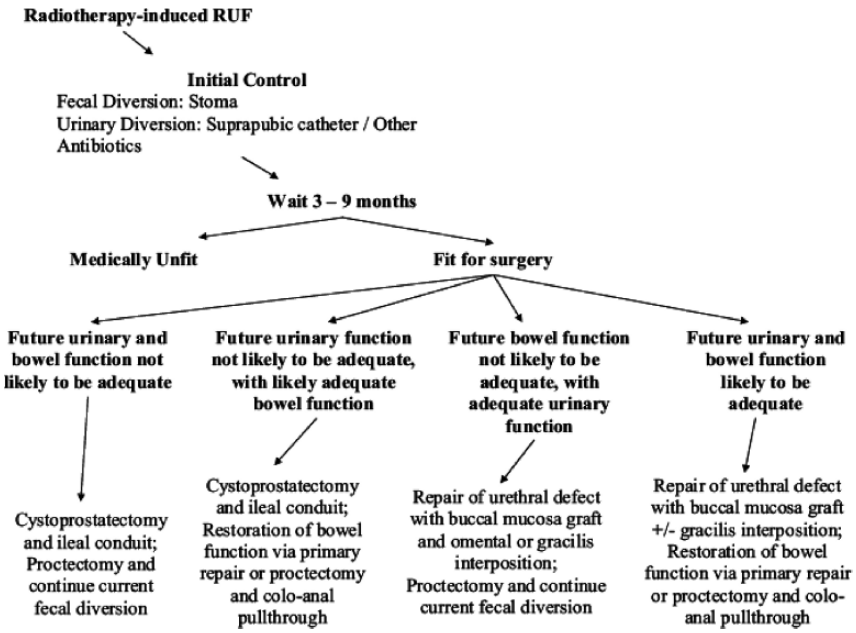


Fig. 6. Algorithm for treatment of radiotherapy induced RUF.

CONCLUSIONS

There is no single best approach to management of RUF. Rather, management in each individual patient should take into consideration fistula etiology, sphincteric integrity, coexisting urethral stricture, functional status of the bladder, extent of rectal damage, fistula size and location, and the overall condition of the patient. In properly selected patients, good outcomes can be expected following transanal or York-Mason repair for small RUF without a history of radiotherapy. Complex fistulas may require the use of buccal mucosa for closure of the urethral defect along with primary rectal repair and gracilis interposition, or alternatively rectal replacement through Turnbull-Cutait colo-anal pull through (Fig. 6).

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24 Hemorrhagic and Radiation Cystitis

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and Raymond R. Rackley, MD

Summary

Hemorrhagic cystitis is the endpoint of a variety of pathologies causing damage to, and diffuse bleeding from, the urothelial lining of the bladder. Etiologies include an array of infections, toxins, pelvic radiation, drugs, and occasionally systemic diseases. In simple as well as complex scenarios, the algorithm for treatment is the same. Underlying causes should be identified and treated, coagulopathies, if present, must be corrected, and supportive care aimed at arresting or controlling the hematuria is instituted. This chapter gives an approach to the various etiologies and management strategies for hemorrhagic cystitis.

Key Words: Hemorrhagic cystitis; hematuria; bladder; bacterial cystitis; bone marrow transplant; radiation; chemotherapy; amyloidosis; anemia; thrombocytopenia.

Contents

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INTRODUCTION

Hemorrhagic cystitis is the endpoint of a wide variety of pathologies causing damage to, and diffuse bleeding from, the urothelial lining of the bladder. The onset may be acute or insidious, and in addition to hematuria, patients often present with irritative voiding symptoms. Etiologies include an array of infections, toxins, pelvic radiation, drugs, and occasionally systemic diseases. All of these disparate pathways converge in the injured bladder transitional epithelium and blood vessels. Urinalysis will reveal large cells with hyperchromatic, oversized nuclei with oddly shaped cytoplasm, and microscopic or gross hematuria. Cystoscopy confirms the diagnosis and may demonstrate a spectrum of injury from minor telangiectatic bleeding to diffuse necrotic ulceration. When severe and relentless, hemorrhagic cystitis can result in constriction of the bladder, anemia, recurrent urinary tract infections, hydronephrosis, bladder perforation, renal failure, and even death. Contributing to this high morbidity is the fact that there is no definitive treatment for all etiologies. Rather, many therapeutic options have been proposed, all with varying levels of success, invasiveness, and adverse side effects. We will discuss the various etiologies and treatments of hemorrhagic cystitis.

ETIOLOGIES

Infection

Bacterial infections rarely cause severe or life-threatening hemorrhagic cystitis. *Escherichia coli* is the leading bacterial cause, followed by *Staphylococcus saprophyticus, Proteus mirabilis*, and *Klebsiella (1)*. Diagnosis is made by urine culture, and the bleeding usually resolves with treatment of the underlying cause.

In addition to bacteria, fungal urine infections can cause hemorrhagic cystitis. *Candida albicans* is the yeast most commonly isolated from urine, accounting for 50–70% of isolates in various studies *(2,3)*. *C. glabrata* and *Candida tropicalis* are the next most common species. Aspergillus fumigatus and Cryptococcus neoformans may also cause fungal hemorrhagic cystitis *(4)*. In urinary infections caused by *C. albicans*, a whitish pseudomembrane or pale elevated plaque covers the urothelium, which may be edematous or ulcerated. Many hospital laboratories do not speciate yeasts that are isolated from the urine unless specifically requested to do so, and this can make treatment and the choice of an appropriate antifungal challenging. It is generally agreed that if the fungal infection is advanced enough to cause hemorrhagic cystitis, then treatment with an intravenous, rather than intravesical, antifungal is warranted.

Parasitic infections may cause severe bladder inflammation and bleeding *(5)*. Although rarely seen in North America, *Schistosoma hematobium* infections are endemic in Egypt *(6)*. The parasite embeds in the bladder wall after entering the bladder muscle through veins in the pelvis. A chronic, eosinophilic inflammatory response occurs, resulting in calcification and fibrosis. Ova are excreted into the urine, causing mucosal hyperplasia and dysplasia that will result in bleeding and the formation of bladder stones. Untreated this may progress to the development of squamous cell carcinoma. *Echinococcus granulosus* infections typically cause calcified cysts in the bladder *(7)*. They may also infiltrate the bladder causing hematuria and hydronephrosis.

Finally, viruses are often implicated as the perpetrators in hemorrhagic cystitis. In the mid-1970s, several outbreaks of adenovirus type 11 were associated with irritative voiding symptoms and gross hematuria in previously healthy Japanese and American children *(8,9)*. In fact, it is the most common cause of hemorrhagic cystitis in the healthy child. More recently, adenovirus type 11 has been implicated in hemorrhagic cystitis following bone marrow and solid organ transplantation, particularly renal transplantation *(10)*. Adenovirus types 7, 21, and 35 have been implicated as well. Diagnosis is generally made by viral culture; however, a more brisk method of diagnosis has been described using a combination of Papanicolaou stain of the urine sediment and transmission electron microscopy *(11)*. The disease presentation can be dramatic, but the course tends to be self-limited and generally resolves within 30 days. As with other types of hemorrhagic cystitis, cystoscopy will reveal diffuse mucosal inflammation.

BK virus, a relative of JC virus, which is the etiologic agent of progressive multifocal leukoencephalopathy, was first isolated in 1971 from a urine sample obtained from a renal transplant recipient. Primary infection is generally asymptomatic and occurs in childhood. After primary infection, the virus can remain latent in many sites, most notably the kidney *(12)*. Reactivation disease is observed in patients with immunodeficiency, particularly HIV-infected patients or those who have received bone marrow or organ transplants. The genitourinary manifestations include hemorrhagic and non-hemorrhagic cystitis as well as tubulointerstitial nephritis and ureteric stenosis *(13)*. Cyclophosphamide-induced hemorrhagic cystitis will be discussed later, but it should be noted that BK virus-induced cystitis tends to be acute, late-onset, and long-duration compared with the early-onset, transient cystitis seen with cyclophosphamide treatment.

An epidemic outbreak of influenza A virus was associated with bladder hemorrhage in 1975 in Tehran *(14)*.

Before treatment, viral cultures should be obtained in all healthy patients who present with hematuria, normal renal function, and negative bacterial cultures. All immunocompromised patients presenting with hematuria, especially those who have undergone either bone marrow or solid-organ transplantation should be evaluated for viral infections.

OXAZAPHOSPHORINE AGENTS

Cyclophosphamide and isophosphamide belong to the family of oxazaphosphorine alkylating agents. They fall under the same classification as nitrogen mustards, which were among the first anti-cancer drugs used in the 1950s. Today, they are used to treat both solid and stem cell cancers. Cyclophosphamide has also been used for a variety of non-malignant conditions including nephritic syndrome, rheumatoid arthritis, lupus erythematosus, polyarteritis nodosa, Wegener's granulomatosis, multiple sclerosis, Crohn's disease, thrombocytopenia, and systemic vasculitis *(15)*. Shortly after cyclophosphamide's introduction, it was noted to cause bladder damage manifested as frequency, urgency, and dysuria with both microscopic and gross hematuria. This may progress into fulminant mucosal necrosis and hemorrhage. In early series, the incidence of cystitis during and after treatment was as high as 68% with a mortality rate of 4% *(16)*. Hemorrhage usually occurs during or immediately after treatment, whether at short-term high or long-term low dosages. Delayed hemorrhage appears to occur in patients treated with long-term therapy.

Philips and colleagues discovered that cyclophosphamide instilled directly into the bladder did not cause cystitis *(17)*. Further study ultimately implicated a metabolic by-product excreted into the urine as the cause of the hemorrhagic cystitis. It was not until 1979 that the culprit, the active metabolite acrolein, was identified *(18,19)*. Within 24 h of a single dose, transmural edema, mucosal ulceration, and epithelial necrosis can be demonstrated with the degree of damage proportional to the dose of cyclophosphamide. The incidence appears to be higher in patients receiving intravenous rather than oral cyclophosphamide and is significantly more severe in dehydrated patients. Thus, initial prevention strategies involved super-hydration. Although acrolein can damage the entire urothelium, the bladder is most affected because of its reservoir function. This affords a longer contact time between the acrolein and the bladder wall, especially if the urine is very concentrated.

Histologic and cytologic studies of patients with acrolein-induced hemorrhagic cystitis show edema, ulceration, neovascularization, hemorrhage, and necrosis. Bladder wash cytology demonstrates small pyknotic or large pleomorphic nuclei in cells that vary widely in size. Edema and hyperemia can be observed within 4 h of administration of the drug and damage progresses for up to 36 h after one dose culminating in necrosis and denudation. The molecular pathogenesis of cyclophosphamide-induced bladder toxicity can be summarized in three steps: (i) acrolein rapidly enters the urothelial cells; (ii) it then activates intracellular reactive oxygen species and nitric oxide production; (iii) finally, the increased peroxynitrite level damages lipids, proteins, and DNA ultimately leading to necrotic cell death *(20)*.

Initially, *N*-acetyl cysteine was used to prevent cyclophosphamide-induced hemorrhagic toxicity. *N*-acetyl cysteine binds the carbon-to-carbon double bond of acrolein, forming a stable, nontoxic compound. Unfortunately, although it is uroprotective, it diminishes the anti-neoplastic effect of cyclophosphamide.

Mesna (2-mercaptoethane sulfonate) was developed specifically to bind acrolein and allow maximum therapeutic effect of the alkylating agent. It was introduced in the United States in 1984 *(21)*. Its toxicity is negligible. It is oxidized to a stable inactive disulfide within minutes of parenteral administration and becomes active when excreted into urine. The medication is now given routinely with cyclophosphamide and iphosphamide chemotherapy for doses above 1000 mg/m^2 *(22)*. Mesna is given in divided doses every 4 h or as a continuous infusion for 18–24 h in a dose equivalent to either cyclophosphamide or ifosfamide. Unfortunately, it does not prevent hemorrhagic cystitis in all patients. Adequate hydration remains the mainstay of therapeutic prevention. In fact, in one study of the bone marrow transplant population, mesna was administered at 160% of cyclyphosphamide dose and was compared with 3 L/m^2 of fluid daily with intravenous furosemide for low urine output *(23)*. Severe hemorrhagic cystitis, defined as the passage of clots and need for medical intervention, was more common in the mesna group (10 vs 6%), and the frequency of either severe or consistent hematuria was 33% in the mesna arm versus 20% in the hydration arm.

RADIATION

Radiation therapy for pelvic malignancies, particularly prostate, cervical, rectal, and bladder cancers, may cause hemorrhagic cystitis either acutely, during treatment, or months to years after the treatment is completed. The hematuria is generally accompanied by symptoms of urgency, frequency, and dysuria. Approximately 20% of

patients treated with pelvic radiation have bladder complications *(24)*. The overall reported rate of radiation cystitis after radiation treatment for prostate cancer is 9–21%, for cervix it is 3–6.7%, and for bladder it is 2–47%. The hematuria may be mild or catastrophic, and it is difficult to predict which patients will suffer this complication.

Diffuse mucosal edema is the first microscopic change noted in biopsies taken immediately after radiation. This is followed by vascular telangiectasia, submucosal hemorrhage, and interstitial fibrosis. Over the long term, this can progress to smooth muscle fibrosis. Bladder capacity diminishes and dysfunctional voiding develops over time as the detrusor muscle is replaced with fibrous deposits. Radiation causes vascular changes as well. Subendothelial proliferation, edema, and medial thickening may progressively deplete the blood supply to the irradiated tissue resulting in an obliterative endarteritis causing acute and chronic ischemia *(25)*. Ulcer formation, radiation neuritis, and postradiation fibrosis may cause the clinical findings of pain and discomfort.

In 1983, the RTOG developed a scale for grading radiation complications as follows:

- Grade 1—Any slight epithelial atrophy, microscopic hematuria, mild telangiectasia
- Grade 2—Any moderate frequency, generalized telangiectasia, intermittent macroscopic hematuria, intermittent incontinence
- Grade 3—Any severe frequency or urgency, severe telangiectasia, persistent incontinence, reduced bladder capacity (< 150 mL), frequent hematuria
- Grade 4—Any necrosis, fistula, hemorrhagic cystitis, bladder capacity < 100 mL, refractory incontinence requiring catheter or surgical intervention
- Grade 5—Death.

There have been many studies addressing both prevention and treatment of radiation-induced hemorrhagic cystitis. Several reports have been published on the use of steroids, vitamin E, trypsin, and orgotein. None have shown a definitive role in either prevention or treatment. The most effective advances in the prevention of radiation cystitis have been in the constant evolution of new delivery techniques and energy sources, which allow for a more narrow focus on the target organ and therefore minimize collateral radiation to healthy structures such as the bladder. The most promising agents aimed at treating radiation-induced hemorrhagic cystitis, both of which will be discussed in the treatment section of this chapter, are sodium pentosulfanpolysulfate (SPP) (Elmiron) and hyperbaric oxygen (HBO). Although therapy is primarily aimed at symptomatic relief, treatment with HBO potentially reverse the changes caused by radiation.

MEDICATION

Rarely, patients treated with members of the penicillin family can develop drug-mediated cystitis (Table 1). Urinalysis and culture reveal sterile pyuria, proteinuria, and to a lesser degree, hematuria. Cystoscopy and biopsy demonstrate diffuse bladder inflammation with marked edema. This class of drugs is well known to cause interstitial nephritis, which may present in a similar fashion. All cases of hemorrhagic cystitis after extended spectrum penicillins were seen in cystic fibrosis patients who had previously been treated with penicillins. Hemorrhage stopped spontaneously when the penicillin was discontinued *(16)*. The pathophysiology of penicillin-related hemorrhagic cystitis has not been defined but may be an immune-mediated sensitivity or a direct toxic effect of the penicillin or one of its metabolites.

Table 1
Causes of Hemorrhagic Cystitis

- A. Infection
  - a. Bacterial
    - i. *Enterobacteriaceae coli*
    - ii. *Staphylococcus saprophyticus*
    - iii. *Proteus mirabilis*
    - iv. *Klebsiella*
  - b. Fungal
    - i. *Candida albicans*
    - ii. *Torulopsis glabrata*
    - iii. *Aspergillus fumigatus*
    - iv. *Cryptococcus neoformans*
  - c. Parasitic
    - i. *Schistosoma hematobium*
    - ii. *Echinococcus granulosus*
  - d. Viral
    - i. Adenovirus 11
    - ii. BK virus
    - iii. JC virus
    - iv. Influenza A virus
- B. Oxazaphosphorine agents
  - a. Cyclophosphamide
  - b. Isophosphamide
- C. Radiation
- D. Medication
  - a. Methicillin
  - b. Piperacillin
  - c. Penicillin GK
  - d. Carbenicillin
  - e. Ticarcillin
  - f. Anabolic steroids
- E. Chemical toxins
  - a. Busulfan
  - b. Aniline and toluidine derivatives
  - c. Thiotepa
  - d. Ether
  - e. Methenamine mandelate
  - f. Gentian violet
  - g. Contraceptive suppositories
- F. Systemic amyloidosis

Even more rare, Andriole and colleagues reported that 14% of 69 patients treated with danazol, a semisynthetic anabolic steroid, for hereditary angioneurotic edema developed hemorrhagic cystitis *(26)*. The reaction was idiosyncratic and related neither to total dose nor to duration of treatment. The bleeding stopped when the danazol was withdrawn. The mechanism by which danazol causes hemorrhagic cystitis in this population is unknown.

Aspirin and nonsteroidal anti-inflammatory medications (NSAIDs) are often overlooked medications that may contribute or cause urothelial cell dysfunction leading to sub-clinical or clinical and pathologic manifestations of interstitial cystitis *(27,28)*. Furthermore, studies have demonstrated that NSAIDs are effective for reducing epithelial proliferation in benign and malignant epithelial malignancies. This may be counterproductive in conditions such as hemorrhagic cystitis, which depend upon urothelium regeneration and proliferation for repair *(29–31)*.

CHEMICAL TOXINS

Busulfan (1,4-butanediol dimethanesulfonate) is an alklyating chemotherapeutic agent used in the treatment of chronic myelogenous leukemia. It can produce a hemorrhagic cystitis similar to that seen with cyclophosphamide; however, the toxicity occurs only after many years of therapy when the cumulative dose of the drug can approach 1 kg. Its mode of toxicity is not through an acrolein metabolite, and there are no known specific preventive or therapeutic treatments. It is suspected to induce bladder epithelial atypia and transitional cell carcinoma *(32)*.

Thiotepa is used intravesically to prevent recurrence of transitional cell carcinoma of the bladder. Rarely, intravesical instillation induces hemorrhagic cystitis *(33)*. It can present as late as 6 months after treatment and is not associated with myelosuppression, the other toxic side effect of thiotepa. In the published case, the mechanism of bladder damage was not elucidated, and other possible causes such as viral infection were not ruled out.

Ether has been used in attempts to deflate Foley catheter balloons with devastating effects on the bladder wall *(34)*. In one case, scarring and diminished bladder capacity persisted for many years after the acute injury leading to long-term irritative voiding symptoms. Inhaled ether does not cause this type of toxicity.

Accidental urethral instillation of *gentian violet* has produced hemorrhagic cystitis *(35)*. Cystoscopy and biopsy revealed edema, mucosal erosion, marked eosinophilia, and non-specific inflammatory changes.

Accidental urethral insertion of *contraceptive suppositories* has been reported to cause a chemical cystitis *(36)*. Cystoscopy in one case revealed an edematous trigone with pancystitis characterizing the rest of the bladder. The causative agent is thought to be nonoxynol-9, a surfactant spermicide. The suppository dissolves in urine within 14 min but because of its acid pH of 3.35, the surface of the suppository may cause mucosal damage before it has a chance to dissolve. Copious bladder irrigation with an alkaline solution, saline, or water is the treatment.

Hemorrhagic cystitis has been reported with overdosages of *methenamine mandelate* when it has been used as a suppressive agent for urinary tract infections *(37)*. Cystoscopy reveals edema and erythema of the bladder mucosa with clear efflux from both ureteral orifices. Direct intravesical instillation of *acetic acid* has been performed for the prevention and treatment of urinary tract infections in patients with either indwelling catheters or who perform self intermittent catheterization. Bladder instillation of 0.25% acetic acid has been found to be safe. Osorio et al. report one case of hemorrhagic cystitis developing after the inadvertent administration of a 2.5% solution, ten times the recommended dose *(38)*. The temporary interruption of instillation led to recovery.

Anilines, toluidines, and their derivatives are well-known urotoxins and known precursors of transitional cell carcinoma. Their use in manufacturing is pervasive

in products ranging from pesticides to shoe polish. They have been implicated in many cases of hemorrhagic cystitis. Exposure to aniline produces methemoglobinemia, methemoglobinuria, hematuria, and dysuria. Hematuria is self-limited and treatment is supportive.

Chlordimeform (*N′*-(4-chloro-2-methylphenyl)*N*,*N*,dimethyl methanimidaminde is a derivative of chloroaniline that is used as a pesticide on cotton crops and fruit trees. Exposure by skin contact, inhalation, or ingestion may cause bladder hemorrhage *(39)*. Biopsies demonstrate epithelial ulceration. Experimental studies have shown that bladder contact with 2-methylaniline, a by-product of chlordimeform, causes bladder hemorrhage. As with aniline toxicity, the hematuria is self-limited and treatment is supportive.

SYSTEMIC AMYLOIDOSIS

Rarely, hemorrhagic cystitis may be seen in patients who have systemic amyloidosis associated with rheumatoid arthritis or Crohn's disease *(40–42)*. Cystoscopy reveals diffuse mucosal bleeding with clear ureteral efflux. Biopsy demonstrates deposition of amyloid in the mucosa, muscle, and vasculature. Instrumentation has been reported to aggravate hemorrhage, and, because bleeding is usually refractory to most treatment regimens, the urologist must be prepared to treat these patients aggressively.

TREATMENT OF HEMORRHAGIC CYSTITIS

It is self-evident that the best treatment of hemorrhagic cystitis is prevention, and various preventive strategies have been outlined for some of the etiologies. However, once a patient presents with hemorrhagic cystitis, the treatment is based more on the severity of the hematuria rather than on the underlying etiology (Table 2). Devries and Frieha have standardized the nomenclature by dividing hematuria into three categories: mild, moderate, and severe *(16)*.

Mild hematuria does not produce an acute decrease in hematocrit and can be controlled with simple measures, such as bladder irrigation with water or saline, silver nitrate or alum. Aminocaproic acid can be effective in treating mild hematuria. HBO therapy is used to treat radiation-induced, mild hemorrhagic cystitis.

Moderate bladder hemorrhage produces a decrease in hematocrit over several days and requires 6 units or less of packed red blood cell transfusion to maintain hemodynamic stability. Patients may develop clot retention. Treatment begins with evacuation of all clots from the bladder followed by continuous bladder irrigation to prevent new clots from forming. Treatment with aminocaproic acid or the more benign intravesical instillations such as alum should be instituted before progressing to formalin therapy. There is a role for intravesical prostaglandin treatment and oral SPP. There are small reports of patients with viral-induced hemorrhagic cystitis responding to intravenous antivirals *(43,44)*.

Severe hematuria is defined by hemorrhage refractory to simple irrigation, instillation, or aminocaproic acid. Greater than 6 units transfusion of packed red blood cells will be required, and these patients may be hemodynamically unstable. Formalin instillation is the most tested agent used to arrest acute, intractable hemorrhage but it has severe side effects. Selective emoblization of the anterior branches of the hypogastric artery is a reasonable and effective option for patients who are too unstable to undergo an anesthetic. Finally, surgical interventions may be required and include placement

of bilateral percutaneous nephrostomy tubes, bilateral cutaneous ureterostomy, ileal conduit urinary diversion, or unilateral ligation of the hypogastric artery.

MILD HEMATURIA

Initially, patients with hematuria should undergo a routine work-up including a detailed history and physical examination as well as the appropriate laboratories to rule out bacterial, viral, fungal, and parasitic bladder infection as well as stones or bladder neoplasms. If an offending pharmaceutical agent is identified, it should be discontinued. Clotting factors such as coagulation panels and platelet counts should be normalized. Certainly aspirin and NSAIDs should be stopped as they contribute to coagulation abnormalities. Additionally, restricting the use of aspirin and NSAIDs should be considered as these agents inhibit prostaglandin synthesis and may prohibit urothelial protection and regeneration. The off-labeled use of misoprostol (cytotec) may provide cytoregeneration of the urothelium when used as an oral or instillation agent *(45)*. Antispasmodics such as oxybutinin or belladonna-opium may provide analgesia.

Evacuation of Clots and Continuous Bladder Irrigation

The mainstay of therapy for bladder hemorrhage is evacuation of all clots within the bladder. Often, this can be accomplished at the bedside through a large lumen catheter. More organized clots may require evacuation through a large caliber cystoscope or resectoscope under direct vision and under anesthesia. The success of all irrigation and instillations rests on the thoroughness of the initial clot evacuation. Operative cystoscopy also allows for the fulguration of any obvious bleeding points. After all

Table 2
Treatment of Hemorrhagic Cystitis

A. Mild Hematuria
  a. Suprahydration
  b. Aminocaproic acid (Amicar)
  c. Hyperbaric Oxygen treatment
  d. Avoidance of prostaglandin synthesis inhibitors (Aspirin and NSAIDs)
B. Moderate and Severe Hematuria (in addition to the above treatments for mild hematuria)
  a. Saline CBI
  b. Alum irrigation
  c. Silver nitrate instillation
  d. Prostaglandin instillation or irrigation
  e. Conjugated Estrogens
  f. Sodium pentosanpolysulphate (Elmiron)
  g. Formalin instillation
  h. Embolization
    i. Surgery
    i. Percutaneous nephrostomy tube placement +/− ureteral occlusion balloons
    ii. Hypogastric artery ligation
    iii. Ileal loop diversion
    iv. Cutaneous ureterostomy
    v. Ureterosigmoidostomy

clots have been evacuated, the prevention of new clots is dependent on appropriately managed continuous bladder irrigation. If the patient can tolerate it from a cardiovascular perspective, oral or intravenous super-hydration can be very effective as well.

Aminocaproic Acid (Amicar)

Systemic aminocaproic acid, administered intravenously or orally, inhibits plasminogen activator, thus inhibiting fibrinolysis. A loading dose of 5 g is given followed by 1.0–2.5 g hourly for a maximum of 30 g in one 24 h period. Doses in excess of 12 g per day do not improve the treatment results. Usually, maximal response will be achieved within 8–12 h. It is particularly important that the bladder be clot-free before starting Amicar as it can make existing clots dense and extremely difficult to remove. Amicar administration is not without side effects and may cause nausea, diarrhea, hypotension, malaise, myopathy, dizziness, headache, intravascular thrombosis, and rarely grand mal seizures. Because of the hypotension and thrombosis, patients with a cardiac history should be carefully monitored.

HBO Therapy

Irradiation of the bladder causes a progressive obliterative endarteritis of the small blood vessels, resulting in cellular hypoxia, bladder ischemia, and fibrosis. HBO treatment may reverse the vascular radiation-induced pathophysiology by causing neovascularization of the bladder wall and so increase tissue oxygen tension and promote healing. At the joint consensus meeting of the European Society for Therapeutic Radiation and Oncology and the European Committee for Hyperbaric Medicine (Lisbon, 2001), it was established that according to evidence-based medicine criteria, the effect of HBO treatment on angiogenesis and osteogenesis in irradiated tissue is graded as Level I *(46)*.

Several authors have studied the use of HBO in patients with radiation cystitis, mainly in retrospective series *(47–51)*. The reported response rate is anywhere from 27–92%. Patients must be stable enough to report to a HBO chamber where they receive 100% oxygen at 2–2.5 atm in 30–60 sessions lasting from 90 to 120 min each. Studies looking at predictors of successful treatment suggest that the severity of the initial hematuria influences the response, with less severe hematuria responding more favorably. Chong et al. suggest that early institution of HBO therapy within 6 months of hematuria onset is associated with greater therapeutic response *(48)*. It bears repeating that HBO is the only therapy that can potentially reverse the damage caused by radiation cystitis.

HBO is usually well tolerated and adverse effects, including visual disturbances, eustachian tube dysfunction, and claustrophobia are uncommon. Acute viral infection is an absolute contraindication as HBO can lead to widespread viremia in this setting. Emphysema, chronic obstructive pulmonary disease, and pneumothorax are relative contraindications. Some diabetic patients may have an exaggerated hypoglycemic response to hyperoxia, the mechanism of which is yet to be defined. In these patients, glucose levels should be monitored.

MODERATE HEMATURIA

Alum

Alum bladder instillation or irrigation is a simple, safe method of chemical cautery first introduced in 1982 *(52)*. The authors described continuous closed irrigation with a 1% alum solution in sterile water, through a large bore, three-way Foley catheter at the patient's bedside, with no general or regional anesthesia. This is essentially the same protocol which is used today. Success rates in two reports involving 13 patients ranged from 50 to 100% *(53,54)*.

Alum works by the astringent action of protein precipitation at the cell surface and superficial interstitial spaces. This leads to decreased capillary permeability, contraction of intercellular spaces, vasoconstriction, hardening of the capillary endothelium and a reduction in edema, inflammation, and exudates. It is not specific to any particular etiology of hemorrhagic cystitis. It is generally well-tolerated, although some patients experience supra-pubic discomfort and bladder spasms. Systemic absorption is minimal; however, in patients with compromised renal function, serum aluminum levels as well as serum pH should be monitored *(55–57)*. The toxicity of aluminum causes neurofibrillary degeneration in the CNS, which manifests as encephalopathy, malaise, speech disorder, dementia, convulsions, and vomiting.

In summary, intravesical 1% alum irrigation for moderate to severe hematuria is generally safe, effective, and well-tolerated.

Silver Nitrate Instillation

Silver nitrate coagulates proteins on the bladder mucosa, resulting in a chemical cauterization. A 0.5–1.0% solution is instilled and remains in the bladder for 10–20 min. This should be followed by a normal saline irrigation to flush out the bladder. The procedure is painful, and the patient will require an anesthetic. In one small series of 10 children with cyclophosphamide-induced hemorrhagic cystitis, bleeding was completely controlled in 90% of patients within 24–48 h of treatment *(58)*. Unfortunately, 8 of these patients recurred. One patient is this series developed anuria secondary to bilateral ureteral obstruction from precipitant from the treatment. Because it requires anesthesia, has a relatively short duration of efficacy, and has potentially serious side-effects, silver nitrate is rarely used today.

Prostaglandin Instillation

Prostaglandin E1, E2, and F2α are natural products of the kidney and bladder and have been used to treat cyclophosphamide-induced hemorrhagic cystitis. In normal bladders, release of these substances from the mucosa is regulated by glutathione, a membrane protectant. The production of prostaglandins is decreased when the bladder is distended, in conditions such as diabetes mellitus, with disruption of normal urine pH and osmolality, and after contact with carcinogens *(59)*.

Several mechanisms have been proposed by which prostaglandins heal a damaged bladder. Prostaglandins strengthen cell membranes, thereby reducing edema. Local vasoconstriction may occur through prostaglandin-stimulated platelet aggregation. PGF2α mediates smooth muscle contractility, which may control bleeding and PGE2 has a cytoprotective effect, which may prevent further damage to the bladder wall.

Carboprost is a commercially available PGF2 F2α, which has been used for intravesical instillation *(60)*. It is instilled as a 0.1–0.4% solution and left in contact with the bladder wall for 25–60 min. The response rate ranges from 60 to 65%. Aside from bladder spasm, this treatment is generally well tolerated and can be done without anesthesia and in patients who are medically unstable. Unlike alum and silver nitrate irrigation, no precipitate is formed which can block ureters or catheters. Disadvantages include the cost and failure to control bleeding in about half the patients.

Conjugated Estrogens

Conjugated estrogens appear to control hematuria by strengthening the capillary walls of the microvasculature in the bladder mucosa *(61)*. Both intravenous and oral-conjugated estrogens have been used successfully in several small trials for patients with hemorrhagic cystitis because of radiation or cyclophosphamide therapy *(62,63)*. Estrogen therapy, particularly long term, should be avoided in patients with a history of thromboembolic events, cardiovascular disease, and cerebrovascular disease because it increases the patient's risk of cardiovascular complications.

Oral SPP

Precisely how SPP controls hematuria is unknown, but it is purported to protect the transitional epithelium by restoring the bladder glycosaminoglycan layer. Recent work also implicated a role for SPP as an anti-inflammatory agent. SPP is an inhibitor of mast cell stimulation and decreases inflammatory response mediators in the transitional epithelium *(64)*. It is administered as 100 mg orally three times per day for a minimum of 4 weeks, or until symptoms resolve. SPP has no detectable anticoagulant activity, is safe and not-toxic *(65)*.

Sandhu et al. recently reported their review of 60 patients with moderate to severe hemorrhagic cystitis where SPP was the primary treatment. Fifty three patients had a history of pelvic radiation and 7 had received cyclophosphamide *(64)*. Of the 51 patients available for follow-up at 4 years, gross hematuria was controlled in 31 patients. As administration requires no anesthetic or specialized equipment and side effects are scant, they recommend SPP as the treatment of choice for managing hemorrhagic cystitis because of either radiotherapy or chemotherapy.

SEVERE HEMATURIA

Formalin Instillation

Formalin is an aqueous form of formaldehyde and was first described by Brown in 1969 as a method of controlling intractable hematuria in patients with inoperable bladder cancer. It exerts its effect on the bladder wall by hydrolyzing protein, thereby coagulating tissue and controlling bleeding in the mucosa and submucosa.

Formalin solution is diluted with sterile water to a concentration of 1–10%; the complication rate increases with increasing concentration. It is instilled in the bladder at a volume of 50 mL or to bladder capacity under general or spinal anesthesia and allowed to dwell for 5–30 min. Anesthesia is required because it causes severe pain. Vesicoureteral reflux should be ruled out by intraoperative cystography. If present, occlusive balloon catheters must be placed in each ureter before formalin instillation to prevent ureteral necrosis, obstruction, and fibrosis. Placing the patient in the reverse

Trendelenburg position may also help to prevent reflux. External skin should be protected with petroleum jelly, and the vagina should be packed to prevent leakage from the catheter.

Formalin is an effective tool for controlling moderate to severe hematuria with success rates of 80–90% *(65)*. However, its efficacy comes at the cost of significant complications. Complications include severe fibrosis leaving a small contracted bladder, urinary incontinence, vesicoureteral reflux, ureteric strictures, vesico–ureteric junction obstruction with hydroureteronephrosis, acute tubular necrosis, vesico-vaginal and vesico-ileal fistula, a toxic effect of the myocardium, and bladder rupture. Five deaths have been reported *(66)*. Because of the potential serious complications, formalin should be used with great caution and only after more conservative measures have failed. The use of a high concentration of formalin (10%) may lead to permanent loss of a functioning bladder and should be avoided in all patients if possible, but particularly in those with a long life-expectancy.

Embolization

Therapeutic embolization of the internal iliac artery for the control of bladder hemorrhage because of radiation cystitis was first reported in 1974 *(67)*. A muscle fragment was used to occlude one internal iliac artery. Since that time, the procedure has been refined and today super-selective embolization to occlude specific regions supplied by very small vessels is possible. As it can be done under local anesthesia and has excellent success rates in the 90% range, this procedure in an attractive option for the unstable patient with intractable hematuria.

The most common complication of embolization is gluteal pain, which can be very severe but usually resolves within several days. In the early days of the procedure, at least two cases of gangrene of the bladder were reported after embolization of one internal iliac artery *(68)*. One patient had transient unilateral lower limb paralysis after the procedure *(69)*. Two theories have been proposed to explain this complication: it is possible that a small emboli could pass from the superior gluteal artery into the spinal arteries through collateral vessels, or the companion artery to the sciatic nerve may be embolized leading to temporary or permanent ischemic damage to the nerve *(66)*.

Surgical Intervention

Surgical control of hemorrhagic cystitis is the last resort for unstable patients with fulminant hemorrhage. If possible, reversible procedures should be exhausted first. Bilateral percutaneous nephrostomy tube placement, with or without ureteral occlusion balloons, diverts urine from the bladder to prevent overdistention and potentially allows a stable clot to form in the bladder and thus self-tamponade. It is rarely associated with life-threatening complications and requires only local anesthesia. In one study from 1993, nephrostomy tubes were placed in 6 patients refractory to initial therapy and 50% had complete resolution of hemorrhage *(70)*.

More invasive surgical options include open ligation of the hypogastric artery and urinary diversion with an ileal conduit, bilateral cutaneous ureterostomy, or ureterosigmoidostomy. In young, otherwise healthy, patients cystectomy should be avoided with the ultimate goal of bladder reconstruction and return to normal bladder function.

CONCLUSION

At a tertiary care center, it is not uncommon to encounter a patient who has recently undergone a bone marrow transplant. As a result of their therapy, they are anemic and thrombocytopenic. They have received cyclophosphamide at some point in their treatment, and they are immunosuppressed and thus may be suffering from any number of infections, particularly viral. In this complex scenario, as well as the patient who presents with a simple bacterial cystitis causing hematuria, the algorithm for treatment is the same. Underlying causes should be identified and treated, coagulopathies, if present, must be corrected, and supportive care aimed at arresting or controlling the hematuria is instituted. The gravity of the clinical situation dictates the intervention.

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25 Infections Due to Anti-Incontinence Devices/Grafts/Slings

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SUMMARY

The use of sling procedures, including bone-anchored slings, is gaining popularity for the treatment of stress urinary incontinence secondary to anatomical disruption of the urinary sphincter following radical prostatectomy and occasionally transurethral prostatectomy. Although the incidence of osteomyelitis as a complication of pelvic surgery is low, careful preoperative and intra-operative use of antibiotics should be employed to achieve the best surgical and post-surgical outcomes and minimization of morbidity. This chapter discusses the signs and symptoms used to diagnose and the modalities used to treat infectious complications.

KEY WORDS: Sling procedure; bone anchored sling; infection; osteomyelitis; urinary incontinence; bladder dysfunction; antibiotics.

CONTENTS

INTRODUCTION

Stress urinary incontinence secondary to anatomical disruption of the urinary sphincter affects a substantial number of patients after undergoing radical prostatectomy and occasionally transurethral prostatectomy. Additionally, intrinsic sphincter

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deficiency may result from a neurological abnormality, such as myelomeningocele. The reported incidence of urinary incontinence after radical prostatectomy ranges from 5% to 60% *(1,2)*. Although detrusor instability may have a role, malfunction of the external urethral sphincter appears to be the primary reason for the incontinence *(3,4)*. Mild degrees of urethral incompetence may be improved or cured with Kegel exercises and pharmacotherapy, whereas more severe incontinence requires more aggressive means to bolster the sphincter mechanism.

Traditional treatments for male stress incontinence after radical prostatectomy include artificial urinary sphincter placement or transurethral collagen injections *(5–7)*. Sling procedures *(7)*, including bone-anchored slings *(6)*, have also been described and are gaining in popularity. The bulbourethral sling procedure uses synthetic bolsters passed beneath the bulbar urethra and suspended from the rectus fascia *(8)*. Initial analyses of this procedure demonstrated a short-term success rate of 85%, preservation of volitional voiding, and no evidence of bladder outlet obstruction. Another surgical option is implantation of a sub-urethral sling achieving ventral urethral compression. Compression can be achieved by suspending the sling under the bulbar urethra and passing sutures through the rectus fascia *(8,9)* or by using bone anchors into the pubic rami *(6,10)*. It is this approach that seems to have the most widespread use in the United States and the experience with infective complications is limited to this current approach.

In this chapter, we give an overview of the infective complications associated with the male sling procedure as it is becoming more widely used. Furthermore, we will discuss the signs and symptoms that a patient may experience, and also the modalities to treat these infections should one occur.

INCIDENCE OF INFECTIONS

The overall prevalence of osteomyelitis complicating all forms of pelvic surgery is 1–3% *(11–16)*. Although the etiology of this complication is multifactorial, the inherent risk of this complication appears to be largely related to the combination of host factors and manipulation of the bone environment and not only to bone manipulation, as proven in previous animal models *(17,18)*.

The undefined potential for the infectious bone anchor complication of osteomyelitis has raised appropriate concerns when adopting this form of stable suture fixation in pelvic reconstructive surgery. Osteomyelitis is well defined as a pyogenic infection of bone and marrow. The major differential diagnosis of osteomyelitis is osteitis pubis, a noninfectious condition that involves the pubic bone, symphysis, and surrounding structures. Although the pathogenesis of osteitis pubis remains controversial *(19)*, periosteal trauma seems to be an important initiating event. The self-limiting nature and response to nonantibiotic therapy indicate that osteitis pubis is a separate clinical entity from osteomyelitis. However, each condition may result from complications of pelvic surgery and may often be misdiagnosed because of a similar clinical presentation.

Although specific indications for the male sling and few adverse predictors have been defined previously, few published data are available addressing this issue *(7,10)*. Short-term success rates for the perineal male sling range between 76 and 90 % *(6,10,20)*.

Male slings have gained popularity using the same concept of urethral compression to achieve continence as in women *(21)*. Later in the 1970s, it became popular as the

Kaufman prosthesis. Although reasonable results were obtained, Kaufman procedure was eventually abandoned because of the problem with erosions and infections. In 1979, Kaufman and Raz reported that 61% of their patients were cured or significantly improved; however, 11% had major complications and 24% had minor complications *(22)*. As opposed to the Kaufman procedure, no dissection was carried out around the urethra and fat and bulbospongiosus muscle were left undisturbed. This prevents direct contact between the urethra and the sling material and may contribute to the absence of erosion following the male sling procedure.

One concern of the male sling procedure is the development of altered bladder compliance secondary to long-standing mechanical compression of the urethra. Hairston and Ghoniem utilized fluorourodynamic studies and demonstrated an increase in Valsalva leak-point pressure without an appreciable change in urethral and voiding pressures in patients undergoing the male sling procedure *(23)*. It appears that extrinsic compression of the bulbar urethra may not lead to significant alteration in bladder function. However, long-term studies are needed to assess the effect of the male sling on bladder compliance. Still, these initial attempts laid the foundation for development of the new bone-anchored male slings that also achieve continence based on ventral compression. Although the nature of the infectious complications is similar in some respects (synthetic graft infections), bone anchoring adds a new potential dimension to this.

In 2002, Comiter reported to have no complications post male sling and the blood loss was also reported to be minimal. There was no instance of infection, erosions, pain, or any de novo urgency or urge incontinence. Some patients developed a mild amount of scrotal numbness that completely resolved in 6 weeks *(10)*.

In 2005, Singla et al. reported in his post male sling complication that one patient developed infection and two developed short-lasting perineal/buttock pain. Significantly, no patient developed urethral erosion *(24)*.

DIAGNOSIS

Because there is a paucity of information regarding male sling infections per se, we compared data published about the suprapubic bone anchor in female patients and correlated the findings. A total of 15 studies describing suprapubic bone anchor placement in 698 procedures indicated 6 cases (0.86%) of infectious osseous complications (Table 1).

Osteomyelitis represents a pyogenic infection of the bone and marrow, and it has been regarded in reviews of the early medical literature as a form of osteitis pubis because of infection. Contemporary classifications of osseous complications recognize osteitis pubis and osteomyelitis as two distinct entities with osteomyelitis frequently misdiagnosed as osteitis pubis after pelvic surgery *(25,26)*. The diagnosis of osteomyelitis is similar to that of osteitis pubis, but the clinical course is progressive. Plain anteroposterior and pelvic outlet radiography, magnetic resonance imaging, and bone scan and computerized tomography detect radiographic changes that range from minimal findings initially to symmetrical superficial bone destruction and a widened pubic symphysis in osteitis pubis that may progress to more irregular, localized bone destruction in osteomyelitis. This sequestration of bone is due to vascular obstruction, suppuration, and necrosis of bony trabeculation. Although bone scan may be positive in each condition of osseous complications, a negative scan generally excludes osteomyelitis.

Table 1
Reported Series of Supra Pubic Bone Anchor Erosions

References	*No. Pts.*	*Mean Mos. Follow up*	*No. osseous infections*
Benderev	150	15	0
Appell, Vasavada et al., Leach and Appell	189	24	1
Haab and Leach	40	18	0
Hom et al.	35	8	0
Jimenez-Calvo et al.	44	11	0
Schultheiss et al.	37	11	2
Batista Miranda et al.	14	12	0
Kane et al.	13	24	0
Enzler et al.	127		2
Tebyani et al.	49	29	1

A review of the case reports of infectious complications because of bone anchor placement in female pelvic floor reconstructive procedures revealed the various organisms isolated from the bone cultures obtained *(26–28)*. They included Pseudomonas, *Staphylococcus aureus*, enterococci, and Citrobacter. The identities of the organisms suggest a possible coliform, skin, or hematogenous source for contamination of the bone anchor site. These organisms are often isolated in case reports and series of pelvic surgery describing the complications of osteomyelitis in the absence of bone-anchoring techniques when an association of abscesses, draining sinuses, and wound and urinary tract infections has been noted *(29–36)*. In addition, patients who had chronic steroid use or immune suppression preoperatively were at a markedly elevated risk for bone infections.

Another potential complication that the surgeon is worried about is the risk of erosion. We believe that the erosion could be due to the pressure created by the sling only on the undersurface of the urethra and allowing the blood to be supplied from

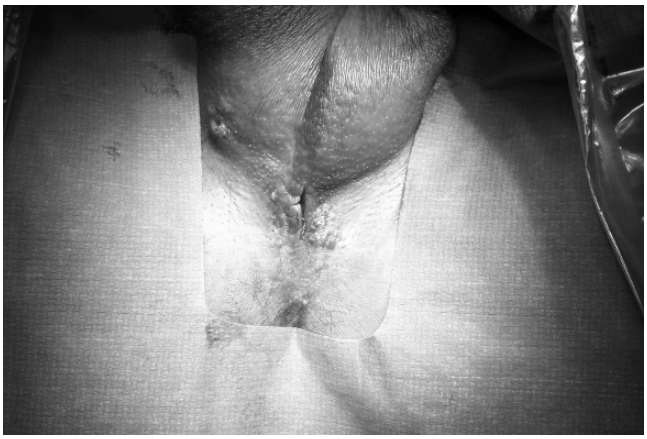

Fig. 1. This figure shows the presence of a sinus tract caused because of postoperative iatrogenic complication.

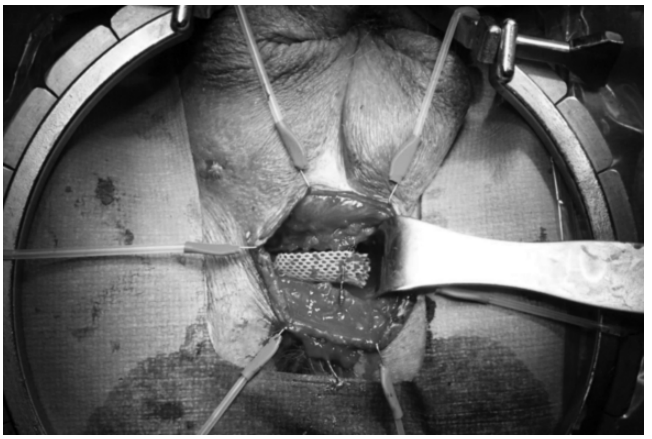

Fig. 2. Shows the dislodgement of the male sling from the original position.

either sides of the urethra. Although no significant data have been published on this, we believe that the surgeon should keep this possible complication in mind despite most techniques demonstrating preservation of the muscle layers around the urethra.

The literature review reveals that there are more infectious complications of bone-anchoring techniques in cases that relied on a suprapubic placement technique compared with transvaginal application. In female cases, when transvaginal bone-anchoring procedures were introduced, many surgeons were concerned about placing a bone-anchoring device that would be passed through a clean-contaminated wound compared with the nearly clean field of a suprapubic wound. Although nearly twice as many procedures have been reported using the suprapubic versus the transvaginal approach, none of the series of transvaginal procedures or case reports describe an infectious complication associated with transvaginal bone anchor placement. Although this finding may represent a reporting bias based on the difference in sample size, the surgical technique used for the two approaches of bone anchor deployment may also explain this unexpected finding. Many initial suprapubic bone anchor series incorporated a high-speed drilling technique for bone anchor placement with the Mitek (Mitek Surgical Products, Inc) and Vesica (Boston Scientific Corp, Natick, MA) bone anchors that may have compromised blood flow to the bone anchor site. Furthermore, the

Table 2
Case Reports of Infectious Complications

References	*Pt. Age*	*Cultured organisms*
Matkov et al.	72	Group B streptococcus
FitzGerald et al.	71	Citrobacter
Enzler et al.	74	Pseudomonas, Staphylococcus
	80	Pseudomonas, Staphylococcus
	71	Citrobacter, gram pos. coccus, gram neg. rods
	76	Staphylococcus

Suprapubic bone anchor fixation was done in all patients.

suprapubic approach typically requires more soft tissue and periosteal trauma because of retractors and/or electrocautery to expose the symphysis for bone anchor placement. Further reports on series without drilling using the Precision-Tac system (Boston Scientific Corp), low-speed drilling with the Precision-Twist and In-Tac (Boston Scientific Corp) techniques of transvaginal anchors or suprapubic anchoring techniques incorporating nondrilling deployment techniques with the Press-In (Boston Scientific Corp) bone anchor system may help to clarify this issue.

THERAPY

Traditional treatment of osteomyelitis has been long-term 4- to 6-week intravenous antibiotics after identifying the offending bacteria by needle aspiration in cases detected early when the blood flow to the symphysis has not been compromised. When detection is delayed and bony changes of necrosis appear, surgical debridement and curettage of the affected bone are needed in addition to antibiotic therapy. Recent reports support the administration of long-term oral antibiotics that achieve high serum and tissue concentrations over intravenous therapy for osteomyelitis. Recommendations for preventing infectious complications of bone anchor placement for pelvic reconstructive surgery are based on two surgical principles. The urinary tract must contain sterile urine to prevent infectious inoculation of the wound site. In addition, antibiotic prophylaxes are recommended in all clean-contaminated (vaginal wounds) procedures, and in all clean (skin) and clean-contaminated (vaginal wounds) procedures involving the insertion of prosthetic or foreign materials *(36)*. Although most male pelvic reconstructive procedures are classified as clean or clean contaminated, those considered contaminated or dirty should not incorporate prosthetics or permanent foreign material. Recommendations for clean and clean-contaminated reconstructive procedures of the genitourinary tract include prophylaxis against Staphylococcus species and expanded coverage for gram-negative and/or anaerobic organisms. Our preferred regimen for antibiotic prophylaxis based on suggested guidelines, patient factors, institutional microflora, and physician experience typically includes combined cefazolin, gentamicin and metronidazole for gram-positive, gram-negative, and anaerobic organisms. Antibiotics are ideally given within 30 min to 1 h before surgical incision. For long procedures, re-administration of the drug is indicated at intervals of 1- to 2-fold the half-life of the agent. Furthermore, the best treatment is truly prevention, and accordingly, we use liberal antibiotic or betadine irrigation intra-operatively to minimize on infectious risk and keep a clean surgical field. Maintenance of good hemostasis is essential to prevention of blood and fluid pockets to preclude a site for colonization of bacteria.

CONCLUSION

Although the prevalence rate of infection because of these procedures is quite low, we adhere to careful preoperative and intra-operative use of antibiotics as the main method to achieve the best surgical and post-surgical outcomes and minimize on morbidity. Furthermore, if these complications are not diagnosed promptly, they could be associated with significant morbidity to the patient.

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26 Indwelling Urinary Catheters

Infection and Complications

Franklin Michota, MD

Summary

Although often a necessary intervention, urinary catheters are the leading cause of urinary tract infection (UTI) in hospitalized patients and are associated with significant morbidity, mortality, and cost. Avoidance of prolonged or any bladder catherization is recommended if possible. Pro-active care should be used to maintain optimal mechanical and antimicrobial operations. Numerous trials of oral antibiotics and urinary acidifying agents, antimicrobial bladder washes, antimicrobial drainage bag solutions, and topical disinfectants confirm that bacteriuria and UTI can be suppressed temporarily, but resistant flora eventually appear. Closed drainage systems remain the cornerstone for preventing catheter-associated UTI.

Key Words: Bacteriuria; bacteremia; biofilm; bladder; nosocomial infection; urinary catheter; urinary tract infection.

Contents

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INTRODUCTION

Each year, over 30 million Americans undergo catheterization of their urinary bladder, with up to 25% of hospitalized patients having a urinary catheter placed at some time during their stay. Indwelling urinary catheters are also commonly used in nursing homes and by about 4% of people visited by home care nurses. Indwelling urinary catheters are a leading cause of morbidity in acute care settings, accounting for up to 40% of nosocomial infections. Within the hospital environment, the intensive care unit (ICU) has the highest prevalence of nosocomial infections with estimated rates of 8–21% for noscomial urinary tract infection (UTI) of which 95% are catheter-associated. The daily incidence of bacteriuria in catheterized patients is approximately 3–10%. Among patients with bacteriuria, up to 25% will develop symptoms of local UTI, and about 3% will develop bacteremia. Catheter-associated UTI (CAUTI) is the second most common cause of nosocomial bloodstream infection. Patients who develop nosocomial UTI have their hospital stay extended by approximately 3 days and are nearly three times more likely to die during hospitalization than patients without such an infection. The case-fatality rate from UTI-associated bacteremia is approximately 13% with severely ill patients at highest risk. The economic consequences of urinary catheter complications are significant, with each episode of hospital-acquired symptomatic CAUTI costing an additional $700 and each episode of catheter-related nosocomial bacteremia costing at least an additional $3000.

INDICATIONS FOR INDWELLING CATHETERS

Indwelling urinary catheters are used for short-term (<14 days mainly in hospitals) and long-term (>30 days mainly in nursing homes and home care) urinary drainage. Urinary catheters are indicated for a variety of reasons, particularly for hospitalized patients (Table 1). However, the use of indwelling urinary catheters is often inappropriate. The use of indwelling catheters was found unnecessary for 58% of patient-days on the general medical ward. In another prospective study, initial catheter insertion

Table 1
Indications for Indwelling Urinary Catheters

Urinary retention
Bladder outlet obstruction
Palliative care
Incontinence
Stage 3 or 4 pressure ulcers on the trunk
Inability to self-catheterize
Poor hand dexterity
Cognitive defects
Measurement of urine output
Patient unable or unwilling to collect urine
Critically ill patients
Surgical procedures with general or spinal anesthesia

was unjustified in 13% of 135 catheterized patients in a medical ICU, with continued catheter use deemed inappropriate in 41% of ICU patient-days. Published recommendations on catheter use are not well understood among clinicians. In addition, physician uncertainty about a patient's medical course or reluctance to reinsert a removed catheter if the clinical situation changes have led to unnecessarily prolonged catheter use. Eliminating the need to change wet clothing or bedding is not an indication for an indwelling urinary catheter, and catheters should not be placed for the convenience of the nursing or medical staff.

Catheters may be used inappropriately because of ignorance of the catheter's presence. Saint and colleagues demonstrated that more than one-third of attending physicians and more than one quarter of resident physicians at four academic medical centers answered incorrectly when asked whether each patient on their service had a urinary catheter in place. For patients without an indication for a urinary catheter, greater than 50% of attending physicians and greater than 40% of senior residents were unaware of the catheter presence. Unfortunately, these catheters often remain in place until either a catheter-related complication occurs or the patient is ultimately discharged.

Computer technology may lend a logical solution to these problems. Computer order entry systems could request an indication for the catheter and prompt an automatic catheter removal date. A recent controlled study of such an ordering system was found to decrease the duration of catheterization by 3 days.

COMPLICATIONS

Mechanical Problems

Discomfort is often described in patients with indwelling urinary catheters, with the majority of men and women relating they can feel the catheter. Over 75% state the catheter is uncomfortable with 50% reporting pain. Non-mobile and male patients are more likely to report discomfort. For the frail elderly, the presence of an indwelling catheter can impair the already limited mobility essentially becoming a "1-point restraint." Catheters substantially reduce patients' ability to function freely, promoting complications such as venous thromboembolism or pressure ulcers.

The use of the smallest size catheter effective for the patient, usually 14 or 16 French with a 5-mL balloon, is recommended. Larger catheters can create patient discomfort, increase the risk of blockage of the periurethral glands, and can further predispose the patient to infection (including epididymitis and prostatitis), urethral irritation and erosion. For long-term catheterization, 10 mL of sterile water should be used for the balloon. Underinflation of the balloon can lead to balloon distortion and catheter deflection with increased risk of blockage and urinary retention. A 30-mL balloon, used most commonly after genitourinary surgery, should not be used for an extended period as it too will increase bladder spasm, urinary leakage, bladder-wall irritation, and greater amounts of residual urine.

Urine leakage around a catheter is common, occurring in 35–65% of patients. Leakage does not indicate the need for a larger catheter, as this will lead to increased bladder and urethral irritation and bladder spasms and can induce urethral and bladder neck dilatation and increased leakage. The catheter itself is a bladder irritant, but other bladder irritants such as caffeine, carbonated beverages, and acidic foods, should be

limited. Patients with indwelling catheters should be on a bowel regimen as constipation can increase urinary leakage around the catheter. Finally, leakage may also be a sign of infection that warrants antibiotic therapy.

Urethral catheter tubing should be secured to avoid tension on the bladder neck as well as accidental dislodgement. Men should have the catheter positioned on the abdomen, and in female patients, on the anterior medial thigh. Gravity dependent, unobstructed drainage of the catheter is one of the most effective measures to prevent infection.

Encrustation with recurrent catheter blockage is common (40–50%) in patients with long-term indwelling catheters (LTC). LTC patients may be classified as "blockers" or "non-blockers." Blockers are patients in whom extensive encrustation consistently and repeatedly develops on their urinary catheters within a few days to a few weeks, resulting in shorter catheter life because of diminished flow and leakage. The most common cause of recurrent blockage is the buildup of mineral salts or encrustations precipitated onto the catheter surface from the urine. These deposits occur both within the lumen of the catheter and on outer surfaces of the tip and balloon that are in contact with urine and may cause pain and trauma during catheter removal. The major components of catheter encrustations are struvite and calcium phosphates, which precipitate from the urine under alkaline conditions. Such conditions occur when the catheter is colonized by microorganisms capable of producing the enzyme urease, such as *Proteus mirabilis* and variants of *Staphylococcus aureus, Pseudomonas aeruginosa, enterococcus faecalis*, Klebsiella species, and other Gram-negative organisms. The enzyme urease from *P. mirabilis* hydrolyses urea six-to tenfold faster than the urease enzymes from other species. Unnoticed obstruction is very dangerous and can cause pyelonephritis, septicemia, and shock within several hours.

Preventing catheter blockage requires proactive care. Most LTC patients classified as "blockers" will have a characteristic pattern of catheter life leading to blockage within a similar time period. Once this pattern is recognized, catheters can be changed at planned intervals to minimize the occurrence of blockage. Hydration and systemic acidification of the urine have not been shown to be effective in reducing the incidence of encrustations. For patients who become blocked very quickly (less than 2 weeks), frequent recatheterization may be unacceptable as well as costly. Catheter encrustations may be dissolved with use of acidic washout solutions. Neutral solutions, such as saline and chlorhexidine are not effective. Strongly acidic solutions will cause inflammatory tissue reactions of bladder mucosa and may limit the frequency with which they may be used. In addition, bladder irrigation can cause bladder mucosa trauma secondary to pressure and suction force. Clinicians should use the smallest volume of washout solution that promotes the extension of catheter life to an acceptable period to patient and caregivers.

Bacteriuria

The bladder is normally a sterile environment with intact host defense mechanisms. Binding of bacteria to normal bladder mucosa triggers an inflammatory response that results in an influx of neutrophils and sloughing of epithelial cells with bound bacteria. The presence of a urinary catheter not only impairs the normal protective mechanisms of the bladder, the catheter itself has no inherent defense against bacteria. The indwelling urinary catheter connects the bladder to the heavily colonized perineum, providing a route for bacterial entry along both the internal and the external surfaces. In

this context, it is inevitable for the bladder to become colonized with microorganisms. In addition, urine often pools in the bladder or in the catheter itself, and urinary stasis encourages bacterial multiplication. Obstruction of the catheter can lead to overdistension and ischemic damage of the bladder mucosa, increasing its susceptibility to bacterial invasion. The presence of bacteria in the urine of an asymptomatic person is termed asymptomatic bacteriuria (ABU) and is distinguished from a symptomatic UTI by the absence of symptoms attributable to infection of the urinary tract.

Microorganism colonization of the urinary tract is a cooperative community termed "biofilm." This is in contrast to the traditionally envisioned bacteria in their free-floating or planktonic state. The structure of biofilm is complex, composed of bacteria cells (10–25%) and polysaccharide matrix (75–90%). The matrix functions as "cement" that holds bacterial cells together and further stabilized adhesion to bladder mucosa. The basic structure is the microcolony of matrix-enclosed communities of bacterial cells, which may include cells of one or many species. The biofilm conveys a survival advantage to microorganisms in terms of their ability to withstand drying, shear forces, ultraviolet radiation, and antimicrobial agents. Conventional laboratory tests in planktonic bacteria may suggest antibiotic-sensitivity in vitro, whereas bacteria within a biofilm are resistant in vivo. The biofilm matrix itself may serve as an antibiotic barrier in some cases. In addition, bacteria in a biofilm matrix are in a slow-growing or starved state; thus, they are not as susceptible to many antimicrobial agents.

An indwelling urinary catheter cannot usually be cleared of a pathogenic biofilm without removing the catheter. As long as the colonized catheter remains in place, biofilm-associated organisms can seed the urine with bacteria. Thus, the most important risk for bacteriuria is the duration of catheterization. Once organisms gain access to the catheterized urinary tract, low-level bacteriuria usually progresses to $> 10^5$ colony-forming units/ml within 24–48 h in the absence of antimicrobial therapy. Open catheter drainage systems lead to bacteriuria in virtually all patients in a matter of days, and they are not recommended. Closed catheter drainage systems (collection tube is fused to the drainage bag) will postpone the development of bacteriuria with a reported daily rate of bacteriuria acquisition of 3–10%. Regardless, the incidence of bacteriuria approaches 100% in individuals who are catheterized for 1 month or longer (LTC patients). Bacteriuria in LTC patients is often polymicrobial with frequent change in organisms. Bladder irrigation, either continuously or intermittently, has not been shown helpful in reducing bacteriuria or UTI if closed drainage systems are employed.

If temporary or long-term urinary collection is required, options other than indwelling catheterization should be considered to reduce the incidence of bacteriuria. Daily intermittent catheterization under sterile conditions may reduce the risk of bacteriuria compared with an indwelling catheter; however, the incidence of bacteriuria is approximately 1–3% per insertion. The literature is mixed on whether continuous external urine collection systems (condom catheters) decrease the risk of bacteriuria and UTI. Suprapubic catheters may be superior to urethral indwelling catheters in preventing urethral damage, such as strictures, and they appear to have a lower rate of bacteriuria and symptomatic UTI than indwelling catheters used in the short term (< 14days). For men, suprapubic catheterization may also reduce the risk of local genitourinary complications such as meatal erosion, prostatitis, and epididymitis. Unfortunately, for LTC patients, suprapubic catheters do not provide more protection for UTI; however, they are associated with greater quality of life.

Symptomatic UTI

The presence of bacteria in the urine does trigger an inflammatory response in terms of pyuria and urinary interleukins, but more than 90% of cases of catheter-associated bacteriuria are asymptomatic. Most cases of ABU should not be treated with antibiotics as the risk of complications from ABU is low, treatment does not prevent recurrence of ABU, and treatment can promote the development of antimicrobial resistance in the patient's flora. Notable exceptions to treating ABU include pregnant women, men with bacteriuria who are about to undergo urologic surgery, and renal transplant patients. Treatment in this setting is intended to prevent complications such as bacteremia, not necessarily to eradicate the ABU. The distinction between ABU and CAUTI must be made on the basis of clinical findings. Approximately 24% of patients with ABU convert to symptomatic UTI.

Symptomatic UTI occurs when bacteriuria leads to either local symptoms of infection (lower abdominal pain or discomfort, flank pain, catheter leakage, change in urine color or character, hematuria), or systemic symptoms (chills, fever, nausea, emesis, confusion, weakness, anorexia, autonomic dysreflexia). In LTC patients, such as the nursing home or spinal cord injury populations, signs and symptoms of infection may be subtle. The presence of fever in LTC patients may not necessarily predict UTI. Pyuria also lacks diagnostic specificity in patients who are chronically bacteriuric. Even urine culture results can be misleading, as numerous studies have shown that urine cultures collected through a chronic catheter will have more species and higher numbers of organisms than urine cultures collected through a newly inserted catheter. Frequently in LTC patients, CAUTI is diagnosed retrospectively when the patient's symptoms resolve in response to targeted urinary tract therapy.

Catheter-associated bacteremia occurs infrequently; yet, consequences can be fatal. Urinary catheter-related bacteremia is diagnosed when the same organism is isolated from both the urine and the blood cultures in the absence of other likely sources of infection. Clinical manifestations of bacteremia may include fever, chills, confusion, hypotension, and leukocytosis. The risk of ABU to bacteremia conversion is approximately 3–4%, and the estimated attributable mortality of urinary tract-related bacteremia is approximately 13%.

Bacteria on the catheter within the protective biofilm matrix may be resistant to antibiotics, so patients with signs and symptoms of UTI should have their catheter changed. Urine should be collected for culture following the change to a new catheter. Treatment of CAUTI in chronically catheterized patients includes 5–10 days of targeted antibiotic therapy. Although a shorter course of antibiotics may be desirable to limit the emergence of resistance, autopsy data suggest a high rate (38%) of coexistent acute renal inflammation in the setting of CAUTI, and a longer course of antibiotics may be required to treat occult pyelonephritis. In addition, there is emerging evidence that uropathogens may persist in a biofilm reservoir within the urinary tract itself, although the implications for treatment in this regard have yet to be fully elucidated. Most CAUTI is monomicrobial with characteristic bacteriology of colonic flora or from the hands of health care personnel (Table 2). The enteric gram-negative organisms found in the catheterized urinary tract are those that are commonly associated with multidrug resistance. Many clinicians empirically start with parenteral antibiotics; however, in the absence of nausea, emesis, or other signs of bacteremia, the benefit of parenteral versus oral antibiotics is not well established. Patients with documented bacteremia should receive at least a 2-week course of antibiotics.

Table 2
Microbiology of Catheter-Associated Urinary Tract Infection (CAUTI)

Escherichia coli
Pseudomonas aeruginosa
Proteus mirabilis
Klebsiella peumoniae
Enterococcus faecalis
Staphylococcus epidermidis
Staphylococcus aureus
Enterobacter coli
Enterobacter aerogeners
Providencia stuartii
Morganella morganii
Candida albicans

Funguria

Funguria, or candiduria, is a common nosocomial condition and may develop as early as the first 2 weeks of hospitalization. An indwelling urinary catheter is a known risk factor for funguria. *Candida albicans* is the most commonly isolated fungal species (40–65%) from the urine, and spontaneous resolution is relatively infrequent. Non-albicans isolates include *C. glabrata* and *C. tropicalis*. Non-pharmacologic measures, such as removing unnecessary antibiotics, and changing or removing the urinary catheter, are typically beneficial but generally inadequate without additional pharmacologic therapy. The most serious complication of untreated asymptomatic funguria is candidemia, which occurs in less than 10% of cases. Intravesical amphotericin B and oral fluconazole therapy are each effective in clearing funguria. Intravesical amphotericin B appears to act more rapidly, but the effect of systemic fluconazole therapy often persists longer than that of amphotericin B irrigation, and oral therapy is more convenient and less expensive.

PREVENTION OF CATHETER-ASSOCIATED URINARY TRACT INFECTION

General Measures

Few effective preventive measures are available for CAUTI. Those strategies shown to be effective are mainly applicable to patients with short-term catheters. Infection control measures to ensure that urinary catheters are maintained properly and removed promptly when no longer needed are the most effective ways to reduce bacteriuria and symptomatic UTI. Sterile technique should be observed for catheter insertion. Drainage bags should be emptied every 4–6 h, at a minimum, to avoid the migration of bacteria in the catheter lumen. Closed drainage systems are recommended at all times; however, many patients out of the hospital with LTC, switch twice daily between bedside drainage bags and leg bags. Cleansing the bag with full-strength distilled vinegar or bleach has been shown to reduce the level of bacteriuria, although the impact on symptomatic UTI is unknown. Rigorous urethral meatal cleansing appears to be of little benefit. Prophylactic antibiotic treatment can reduce symptomatic UTI; however,

they are associated with a high rate of selection of resistant species and are generally not recommended. Furthermore, frequent courses of antibiotics subject patients to possible adverse drug effects and suprainfections such as *Clostridium difficile* colitis. Due to a lack of data, rigid schedules for catheter changes are not recommended in favor of an individualized symptom-guided approach. Meta-analysis data on the consumption of cranberry products (juice or capsules) have been shown to reduce the incidence of recurrent UTI in non-catheterized women, but there is little evidence for benefit in men or in patients with an indwelling urinary catheter. Intravaginal estrogen can reverse urethral and vaginal atrophy, increase vaginal moisture, and decrease vaginal pH, and is helpful in improving patient comfort and decreasing the incidence of UTI in postmenopausal women with indwelling catheters.

Biofilm disruption

Because biofilm is the central factor in the pathogenesis of CAUTI, strategies designed to prevent biofilm formation with novel catheter coatings are currently being investigated. No surface is expected to resist biofilm formation in the urinary tract indefinitely, but impeding biofilm development may suffice if the catheter is intended for short-term use. Antimicrobial impregnated catheters with silver alloy have been shown to termporarily delay the onset of bacteriuria compared with latex or silicone catheters. However, these catheters are more expensive than are systemic antimicrobial prophylaxis, which can have the same effect. In addition, resistance to silver is likely to become a problem with widespread use. This has been demonstrated in environments where silver antiseptics are used frequently such as burn units. These concerns are applicable to other agents used to impregnate urinary catheters, including chlorhexidine and nitrofuroxone.

Another approach is to create a catheter surface that scavenges nutrients, particularly iron, that are necessary for biofilm growth. Adding lactoferrin, a host-derived iron-chelating agent, to bacterial cultures can prevent formation of biofilm microcolonies. Such catheters have not yet been developed for clinical trials.

Many new and older substances are currently being tested to disrupt biofilm. Biofilm-associated bacteria produce quorum-sensing signal molecules that regulate expression of genes essential to biofilm formation. Mutant strains of bacteria that cannot produce these signals are able to adhere to surfaces but are unable to differentiate into a biofilm community. Disruption of quorum-sensing through inhibitors have been studied in animal models and hold promise for the future. Coating catheters with older agents, such as heparin, *N*-acetylcysteine, and aspirin, have also been shown in small pilot studies to delay biofilm development, but remain investigational at present.

Bacterial Interference

The goal of bacterial interference is to use benign organisms to form a catheter-associated biofilm, preventing colonization and symptomatic infection with pathogenic organisms. Bacterial interference avoids the use of antimircrobial agents and the attendant potential problems of resistance. Deliberate instillation of a benign strain of *Escherichia coli* 83972 into the neurogenic bladders of persons with spinal cord injury confirmed that direct bladder innoculation was safe, did not produce symptoms of UTI, and reduced the frequency of UTI as compared with the patients' historical

baselines. Furthermore, *E. coli* 83972 impregnated catheters have been shown to impede catheter colonization by uropathogens. Prospective trials involving both direct bacteria-instillation and bacteria impregnated catheters are ongoing.

CONCLUSIONS

Indwelling catheter use is widespread in both acute and non-acute care settings in the United States. Although often a necessary intervention, urinary catheters are the leading cause of UTI in hospitalized patients and are associated with significant morbidity, mortality, and cost. Avoidance of prolonged or any bladder catheterization is recommended if possible. For those who require indwelling urinary catheters, there are few effective preventive strategies. Numerous trials of oral antibiotics and urinary acidifying agents, antimicrobial bladder washes, antimicrobial drainage bag solutions, and topical disinfectants confirm that bacteriuria and UTI can be suppressed temporarily, but resistant flora eventually appear. Closed drainage systems demonstrated effectiveness in reducing bacteriuria and infection over four decades ago and remain the cornerstone for preventing CAUTI today.

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27 Pain and Inflammation Associated with Genitourinary Prostheses

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Summary

Chronic pain after genitourinary prosthesis (penile, artificial urinary sphincters, and testicular) implantation is most often associated with infection or erosion. Management of infected or eroded devices requires device removal. Chronic pain in the absence of infection or erosion is rare.

Most genitourinary prostheses are made with silicone or silicone elastomer. In the past, testicular prostheses usually contained silicone gel but today they do not. The controversy surrounding silicone breast implants and connective tissue disease is discussed. There is no significant evidence linking genitourinary prostheses and connective tissue disorders.

Key Words: prostheses and implants; prosthesis-related infections; penile prosthesis/adverse effects; urinary sphincter, artificial; silicones/adverse effects; pain, chronic

Contents

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INTRODUCTION

Pain in the immediate postoperative period is a normal occurrence after most operations and procedures to implant genitourinary prostheses are no exception. This chapter will address the causes and management of prolonged or chronic pain following implantation of genitourinary devices.

SEARCH STRATEGY

A search from 1966 to present was conducted in Ovid Medline and Scopus. The search was done by an experienced medical librarian using the exploding subject headings: penile implants; urinary sphincter, artificial; and also testis and scrotum. These were then combined with "prostheses and implants" and "surgically-created structures" (both terms were also exploded); these same terms were then again combined with pelvic pain; low back pain; pain, intractable; pain; and pain, postoperative (all exploded). Using these subject headings, the librarian text-worded the terms "chronic," "long term," and "chronic disease." Only three references were encountered using this search methodology. Thus, there is little published knowledge concerning prolonged or chronic pain following genitourinary prosthesis implantation. The majority of the information in this chapter comes from the author's experience as an urologist who has implanted genitourinary prostheses from 1973 to present. This experience encompasses implantation of more than 1500 penile devices, more than 700 artificial urinary sphincters, more than 50 testicular prostheses, and numerous prosthesis revision procedures.

PENILE PROSTHESES

We perform penile prosthesis implantation in an outpatient surgical center under either general or spinal anesthesia. Patients are sent home after an overnight stay. We give most patients a single prescription for fifty tablets containing oxycodone 5 mg and acetaminophen 325 mg. The patient is instructed to take 1 or 2 tablets every 4–6 h as needed for pain. Most men use this medication but do not request a second prescription as they are able to control their postoperative pain by switching to a non-steroidal anti-inflammatory agent. The amount and duration of postoperative pain varies in penile prosthesis recipients, but most men experience discomfort for about 2–4 weeks.

Infection and Erosion

The most common cause of chronic pain following penile prosthesis implantation is infection. Infection occurring in the early postoperative period (within days to weeks) is usually because of gram-negative bacteria *(1)*. In addition to pain, these infections are usually associated with fever, erythema, and wound drainage. Infections because of gram-positive organisms such as Staph epidermidis, Staph aureus, and Staph sp. usually become evident much later (6–12 months) and are first heralded by pain *(2)*. Typically, the usual postoperative pain never fully resolves. Fever, erythema, and wound drainage are usually absent; thus, persistent pain is often the only symptom present. Most commonly, the only physical sign is adherence of the scrotal skin to the underlying pump. With time the adherent skin becomes thinner and eventually the pump erodes through the scrotum (Figure 1). The scrotal pump is the most common

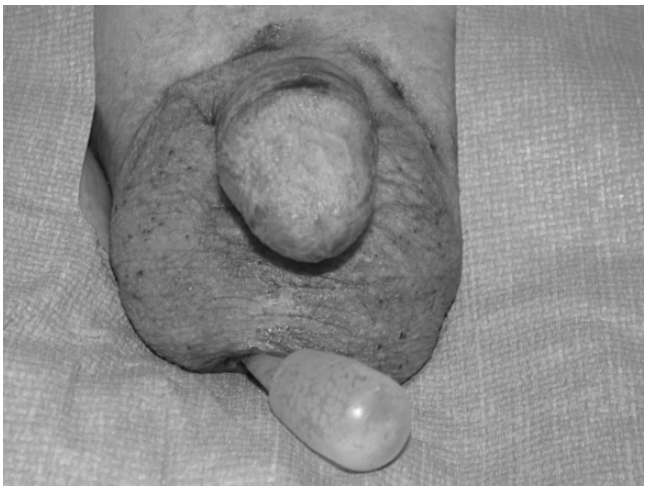

Fig. 1. Scrotal pump erosion in a man who has an infected inflatable penile prosthesis

site where infection is first evidenced because this portion of the prosthesis is closest to the body surface.

Historically, the incidence of infection in primary (first time) penile prosthesis implant surgeries has ranged from 1 to 3%, but in secondary (revision) implant surgery, it was considerably higher (7–18%) *(1, 3–5)*. It was common in the 1970s and 1980s when devices failed in a relatively short time after implantation to replace only the failed components of the device. Today, prosthesis mechanical reliability is considerably better, and device failure before 5 years is uncommon. Hence, the usual practice is to remove the entire device, irrigate thoroughly with antibiotic solution, and then implant a new device. When this is done, the infection rate does not differ significantly from the infection rate seen with primary implants *(3,6)*.

When prosthesis infection is suspected, treatment with broad spectrum antibiotics almost always results in temporary resolution of symptoms; however, antibiotics alone will almost never permanently eliminate this type of infection. The harboring of microorganisms in a biofilm that adheres to the device is felt to be responsible for the failure of antibiotic treatment alone in this setting *(7)*. Early in the history of prosthetic surgery, just the scrotal pump was removed because this was usually the only part of the prosthesis where infection was evident. Later, infection of the remaining portions of the implant would become evident, and we now realize that from the onset the entire device is infected and all components need to be removed.

Organic erectile dysfunction (ED) secondary to diabetes mellitus is a common reason for penile prosthesis implantation. We have found no evidence for a significant difference in the infection rate of diabetic and non-diabetic penile prosthesis recipients *(6,8)*. Wilson et al. did find an increased rate of infection in diabetic implant recipients compared with that in non-diabetic implant recipients; however, there was no statistically significant increase in infection with increased levels of gylcosylated hemoglobin *(9)*. This is in contrast to Bishop et al. who found increased infection in diabetics with glycosylated hemoglobin above 11.5% compared with diabetics with glycosylated hemoglobin below 11.5% *(10)*. Evidence is thus divided as to whether

and to what degree diabetes mellitus increases the infection risk of penile prosthesis implantation.

For many years, the management of infected penile prostheses involved removal of the entire prosthesis with prosthesis reimplantation at a later date after complete healing and resolution of infection. Device reimplantation with respect to placing a new abdominal fluid reservoir and a new scrotal pump is not particularly difficult. Placing new cylinders into each corpus cavernosum can be, however, quite challenging. The penile prosthesis infection results in death of varying proportions of the cavernosal smooth muscle with conversion to scar (fibrosis). With maturation, the scar contracts making the penis smaller and cylinder placement at the time of the second surgery quite difficult. Often special surgical techniques are needed *(11,12)*.

Mulcahy and associates in 1996 introduced the concept of the salvage procedure for infected penile prostheses *(13)*. In the salvage procedure the entire prosthesis is removed, cultures are obtained from the material around the device components, and then all component compartments are irrigated with multiple antibacterial solutions. A new prosthesis is implanted, and the patient is placed on long-term antibiotics. In an update on this procedure, Mulcahy's group reported that of 55 patients available for follow-up, 45 (82%) were free of infection *(14)*. Successful salvage procedures maintain penile size and correct the problem with only one operation.

In 2001, American Medical Systems (AMS) introduced InhibiZone™, an antibiotic coating of rifampin and minocycline, in its inflatable penile prosthesis product line. Early experience showed a reduction in infection rates from 1.61% in non-InhibiZone-coated devices to 0.68% in devices coated with this antibiotic combination *(15)*. Mentor Corporation in 2002 introduced a hydrophilic polyvinylpyrrolidone coating for their inflatable penile prosthesis (Mentor Titan™). The surgeon places this coated prosthesis in an antibiotic solution and the hydrophilic coating allows antibiotics to transfer to the surface of the prosthetic device. Use of this coating resulted in a reduction of the infection rate from 2.07 to 1.06% *(16)*.

Other Causes of Pain

Chronic, unexplained pain is rare in our experience. We have removed only two penile implants because of chronic pain in the absence of infection. One was in an individual with organic ED as the result of multiple surgical procedures to remove a sacral chordoma. This patient had severe burning pain, which was not decreasing in intensity, and at his request, the penile prosthesis was removed 6 months after implantation. All intraoperative cultures were negative. The pain resolved immediately after device removal. Presumably, this pain was secondary to a sensory neuropathy.

The second patient had organic ED secondary to vascular disease. At his request, the prosthesis was removed 14 months after implantation. No infection was evident and cultures from cylinder, pump, and reservoir sites were negative. His pain did not resolve following the removal of the prosthesis. This pain remains unexplained and may have been due to psychogenic causes.

Occasionally, penile prosthesis recipients who have diabetes mellitus experience a burning type of pain after prosthesis implantation. This pain commonly takes longer than usual to resolve; however, in all cases thus far, pain in diabetic recipients who do not have infection has resolved. We have not had to remove any devices because of unexplained pain in these individuals.

In men who receive a non-inflatable, malleable penile prosthesis, if the device is too long, erosion may occur. In the absence of erosion, chronic pain may result. Removal of the too-long malleable device and replacement with a shorter malleable implant or an inflatable penile prosthesis invariably results in resolution of the pain.

Sensory Loss

Most men with organic ED have difficulty attaining or maintaining erections. Sensation, orgasm, and ejaculation are usually intact. Penile prosthesis implantation treats the ED and does not ordinarily interfere with sensation or the ability to reach orgasm and ejaculate.

Inflatable penile prosthesis implantation is performed by one of two approaches: penoscrotal (under the penis at its junction with the scrotum) or infrapubic (just above the penis). The dorsal nerves, responsible for penile sensation, are on the dorsal side of the penis and may be injured at the time of penile prosthesis implantation or revision surgery when the infrapubic approach is used. This is particularly true when the monopolar cautery is used to open the corpora. The exact incidence of dorsal nerve injury is not known; however, it is relatively uncommon. With complete bilateral dorsal nerve injury, there is little or no sensation in the penis. Partial dorsal nerve injury results in impaired sensation. Unfortunately, if dorsal nerve injury occurs, no treatment is available. An advantage of the penoscrotal approach is that the surgery is performed on the ventral aspect of the penis where this complication is avoided.

ARTIFICIAL URINARY SPHINCTER

The artificial urinary sphincter (AUS) was introduced in 1973 *(17)*. Initially, it was implanted in men, women, and children with severe urinary incontinence. Today, its primary use is in the treatment of postprostatectomy urinary incontinence *(18,19)*.

As with penile prosthesis implantation, persistent pain following AUS implantation is most often due to infection. In the case of the artificial sphincter, cuff erosion into the urethra may also be a cause of persistent or recurrent pain. When the AUS sphincter is implanted to treat incontinence after radical prostatectomy, infection occurs in 1.4% of patients and urethral cuff erosion occurs in 4% *(20)*. When infection occurs, the entire device should be removed with AUS reimplantation planned for a later date. Antibiotic coatings for the AUS are not currently available.

For urethral cuff erosion, we recommend complete AUS removal. A urethral catheter should be left for 3 weeks to serve as a stent during healing. AUS implantation at a later date after urethral erosion is facilitated by the transcorporal cuff approach *(21)*. The management protocol for AUS infection without cuff erosion is the same except that a stenting catheter for the urethra is not required. AUS cuff erosion, in addition to sometimes causing pain, also frequently presents as recurrent incontinence. The management of persistent or recurrent incontinence after AUS implantation has been formalized *(22)*.

TESTICULAR PROSTHESES

Testicular prostheses are available to boys and men who are missing one or both testes. Of course, the testicular prosthesis has no function and only restores normal appearance. Today's implants are remarkably life-like.

In a survey of 488 surgeons concerning complications of testicular prosthesis implant surgery, 387 surgeons reported placing 3031 implants. The following complications were reported: wound dehiscence (4.1%), persistent scrotal contraction (3.2%), chronic pain (1.3%), infection (1.0%), and hematoma (0.8%) *(23)*. Extrusion occurred most often in men who had prostheses placed after epididymo-orchitis and in those cases where the incision overlies the prosthesis.

SILICONE

The AUS and most penile and testicular prostheses are made of silicone or silicone elastomer *(24)*. For some time, there was a controversy about whether silicone breast implants, particularly those filled with silicone gel, were related to connective tissue disorders *(25)*. Large cohort studies, however, have failed to show any association between these two entities *(26–28)*. Although silicone particles have been found in the capsule and regional lymph nodes of patients undergoing revision penile prosthesis or artificial urinary sphincter surgery *(29)*, there has not been any evidence that this causes disease. Furthermore, silicone gel, which has been suggested as being related to connective tissue disorders, is not present in the AUS or any penile prosthesis. One study of 34 testicular implant recipients with a mean follow-up of 5 years showed no evidence of connective tissue disease *(30)*. In another study of testicular silicone gel prosthesis recipients, serological tests showed immunological alterations in 5 of 7 prosthesis recipients; however, the study design did not allow a conclusion to be made regarding the significance of these findings or whether they were associated with the testicular implant *(31)*. Because of controversy surrounding silicone gel, which leaks into the body if a breast or testicular implant ruptures, most of these implants today are filled with saline, or in the case of some testicular implants are made of solid silicone.

CONCLUSIONS

Chronic pain after genitourinary prosthesis implant surgeries is uncommon. When present, it is almost always associated with infection or erosion.

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