

## Etiology of testicular pain 2019: Classification into ten logical subgroups

### Etiología del dolor testicular 2019: Clasificación en diez subgrupos lógicos

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#### Abstract

**Background:** Testicular pain encompasses a vast medical diagnostic field, with numerous organ and system convergence. Acute testicular pain is a medical emergency that requires accurate evaluation and immediate resolution, whereas chronic testicular pain is enigmatic and requires sound knowledge of the mechanisms of testicular pain and the differential diagnosis.

**Objective:** To review the causes of testicular pain and propose a new etiologic classification consisting of 10 subgroups.

**Methods:** A bibliographic search was carried out utilizing Google and the National Library of Medicine's PubMed databases to identify original articles and review articles (hard copy or electronic) published on testicular pain, up to March 2020. The search included: MeSH terms: testicular disease (classification, complications, etiology, trauma, microbiology, pathology, pathophysiology, secondary, surgery, treatment) and vasectomy; Non-MeSH terms: acute and chronic orchialgia, scrotalgia, orchidynia, groin pain, epididymalgia, testalgia, chronic testicular pain, chronic scrotal pain syndrome, testicular pain syndrome, epididymal pain syndrome, and post-vasectomy pain syndrome. The initial search produced 625 articles, of which 143 were included in the present review.

**Results:** To better understand testicular pain etiology, 100 possible diagnoses were divided into ten subgroups: infectious, neoplastic, traumatic, torsional, vascular, immunologic, neurologic, pharmacologic, obstructive, and miscellaneous causes. Likewise, treatment can be divided into two main groups, according to therapeutic options: pharmacologic and non-pharmacologic, with the latter subdivided into: noninvasive and the increasingly performed invasive (surgical) alternatives.

**Conclusions:** Testicular pain should be understood as a complex pain syndrome of enigmatic origin. Treatment success depends on the correct identification, from hundreds of possibilities, of the cause of pain. Logical grouping of those possibilities could aid in making the accurate etiologic identification.

#### Keywords:

Pain, Acute pain,  
Chronic pain, Visceral  
pain, Scrotal pain,  
Testicular pain,  
Orchialgia

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**Citación:** Uribe-Arcila J. F., Delgado-Montoya A., Gaviria-Gil F. *Etiology of testicular pain 2019: Classification into ten logical subgroups*. Rev Mex Urol. 2020;80(4):pp 1-19

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Recepción: July 4, 2019

Aceptación: July 26, 2020



## Resumen

**Introducción:** El dolor testicular es un vasto campo de diagnóstico médico, donde convergen múltiples órganos y sistemas. El dolor testicular agudo es una emergencia médica que necesita una evaluación adecuada y una resolución inmediata; pero cuando aparece como un problema crónico, se convierte en un enigma que requiere un buen conocimiento de los mecanismos del dolor testicular y el diagnóstico diferencial.

**Objetivo:** Revisar la etiología del dolor testicular y proponer una nueva clasificación en diez subgrupos etiológicos.

**Método:** Se realizó una búsqueda bibliográfica en Google y las bases de datos National Library of Medicine's PubMed para identificar artículos originales y de revisión, publicados o publicados electrónicamente, sobre el dolor testicular, hasta marzo de 2020. Los términos de la búsqueda incluyeron: Términos MESH: Enfermedad testicular (Classificacion, complicaciones, etiologia, trauma, microbiologia, patologia, fisiopatologia, secundaria, cirugía, tratamiento) y vasectomia. Términos No MESH: orquialgia aguda y crónica, escrotalgia, orquidinia, inguinalgia, epididimalgia, testalgia, dolor testicular crónico, síndrome de dolor escrotal crónico, síndrome de dolor testicular, síndrome de dolor epididimario y síndrome de dolor post vasectomía. La búsqueda inicial produjo 625 artículos y 145 se incluyeron en la presente revisión.

**Resultados:** De 100 diagnósticos posibles, para comprender mejor la etiología del dolor testicular, se pueden subdividir en diez subgrupos: infecciosos, neoplásicos, traumáticos, torsionales, vasculares, inmuno-lógicos, neurológicos, farmacológicos, post obstrucción y causas diversas. Asimismo, el tratamiento se puede dividir en dos grupos mayores según las opciones terapéuticas: tratamiento farmacológico y no farmacológico, este último con una subdivisión: opciones no invasivas e invasivas (quirúrgicas) que se están expandiendo.

**Conclusiones:** El dolor testicular debe entenderse como un síndrome doloroso complejo con un origen enigmático. El éxito del tratamiento depende de la correcta identificación de la fuente del dolor; con un centenar de causas posibles, el uso de una agrupación lógica podría facilitar esta identificación.

## Palabras clave:

Dolor, Dolor agudo, Dolor crónico, Dolor visceral, Dolor escrotal, Dolor testicular, Orquialgia

## Introduction

Testicular pain is a constant reason for urology consultation. All medical professionals must be fully equipped with a powerful diagnostic vision that requires an open mind and healthy skepticism, to prevent falling into the common limitations of clinical judgment. Lack of awareness of the differential diagnosis can lead to errors and confusion with other diseases that share similar symptoms but have different causes and pathophysiology. Therefore, the present review aims to provide an updated inventory of the different and ever-changing diagnostic and therapeutic options.<sup>(1-3)</sup>

### History of Testicular Pain

Testicular pain has been a human concern throughout history. In ancient Greek mythology, the testes were the preferred human body parts utilized by the gods for tormenting men. Castration was a religious and medical practice for more than 3000 years and is recorded in the old testament. Castrated men, called eunuchs, were employed in imperial palaces to guard the royal harem. In the 16th and 17th centuries, prepubescent boys were castrated so they could remain choir singers, known as castrati, retaining their clear, high, childlike voices.

In 1703 Giovanni Batista Morgagni (1682-1771), considered the father of European anatomy, was the first to describe a hydatid of the testis, while he was the surgical assistant to Antonio Maria Valsalva at the hospital of *Santa Maria della Morte* in Bologna, Italy. Hydatid means “drop of water” and Morgagni went to his grave convinced that the rupture of those structures, which now bear his name, explained

the genesis of hydroceles. In 1776, John Hunter, an English surgeon, first reported a case of testicular torsion, and 137 years later, Louis Ombrédanne, one of the founders of pediatric surgery, described testicular appendage torsion in 1913. In 1922, Colt considered testicular torsion a surgical emergency.<sup>(4-6)</sup>

### Neuroanatomy of the Scrotal Contents

Sensory innervation of the testis and epididymis is conducted by autonomic and sensory fibers that travel through the spermatic cord. The somatic fibers of the cremaster muscle and the parietal and visceral layers of the tunica vaginalis travel via the genital branches of the genitofemoral nerve (originating in L1-L2) and ilioinguinal nerve, arising from the first lumbar spinal nerve (L1). Testicular nociceptive fibers travel via the sympathetic plexus (T10 to T12), whereas the deferential and epididymal nociceptive fibers travel via the pelvic plexus (T10 to L1) throughout the vas deferens.<sup>(7-9)</sup>

### Classification of Pain (Origin)

The term orchialgia can often cause some level of confusion, since it suggests an exclusively testicular origin (orchio-: testis). In fact, the origin of intrascrotal pain can be perceived in the inferior part of the abdomen, the internal inguinal ring, the penis, the back, or the upper part of the thighs, and not necessarily in the testicular body, whereas in some extrascrotal pathologies, the painful sensation is directly in the testis and its vicinity, altering patient quality of life. Other more descriptive medical terminology has been employed, such as scro-

talgia, orchidynia, groin pain, epididymalgia, testalgia, testicular angina, chronic testicular pain (CTP), chronic scrotal pain syndrome (CSPS), chronic unexplained orchialgia, and enigmatic syndrome, but they all appear to be equally incapable of conveying the complexity of this painful phenomenon. The testes (and breasts and eyes) are the only organs of the body that exhibit the three basic types of pain: somatic, visceral, and neuropathic:

- **Somatic:** Somatic pain receptors are found in the skin, muscles, and joints. They can be subdivided into superficial receptors, in which the stimulus affects skin receptors, and deep receptors, in which the stimulus is received in the muscular planes, connective tissue, or bones.
- **Visceral:** The visceral nociceptors, which are mainly composed of unmyelinated afferent fibers, are activated by traction, distension, or ischemia. Pain is diffuse and dull. It has an independent component that allows it to be sent through a cutaneous area that shares the same innervation pathway.
- **Neuropathic:** The original definition of neuropathic pain is “that which originates in injury or dysfunction of the nervous system”. Ever since this first definition, it has undergone constant changes because neuropathic pain is not a single disease, but rather a broad spectrum of signs and symptoms that alter patient well-being. Its definition was later modified to be closer to the pain characteristics previously described. The International Association for the Study of Pain currently defines it as: “pain caused by a lesion or disease of the somatosensory nervous system.”

In that type of pain, the afferent peripheral nerve fibers respond to the stimulus by

activating a biochemical cascade that includes potassium release, sodium channel alteration, and prostaglandin and bradykinin synthesis. Activation causes impulses from the stimulated terminals to spread across the dorsal horn of the spinal cord and other adjacent nerve terminals before it achieves supraspinal neuromodulation. Those terminals induce the release of prostaglandin E2, bradykinin, cytokines, chemokines, and neuromodulators, such as P substances, that cause vasodilatation and neuronal edema, resulting in an increase of histamine and serotonin concentrations in the extracellular fluid, sensitizing all neighboring nociceptors and causing an erratic dissemination of painful sensation. Patients often experience 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). That repeated process explains the genesis of chronic testicular pain. The pain can be exacerbated by cycling, driving, sitting, horseback riding, or by wearing clothing.<sup>(10-12)</sup>

### *Testicular Pain (Classification)*

- a) Acute orchialgia presents with pain that lasts less than seven days. However, it very frequently constitutes a urologic emergency, requiring immediate evaluation and treatment, hence acute scrotum is an appropriate designation. Epididymitis is considered a temporal exception, since, by definition, it is considered an acute diagnosis, with a less-than-six-week progression.

From the seventh day (acute pain) to the sixth month (chronic pain), some conditions may be considered subacute and may arise from any of the causes reviewed herein.<sup>(13)</sup>

b) Chronic orchialgia is constant or intermittent testicular pain that lasts more than six months. All causes of acute pain are potential causes of chronic pain, when patients do not receive adequate diagnoses and treatment.<sup>(14)</sup>

The European Association of Urology (EAU) differentiates four separate syndromes in its guidelines on chronic pelvic pain:<sup>(15)</sup>

- Scrotal pain syndrome is the experience of persistent or recurrent episodic scrotal pain that is associated with urinary tract or sexual dysfunction symptoms. There is no epididymo-orchitis or other obvious pathology.
- Testicular pain syndrome is the experience of persistent or recurrent episodic pain located in the testis upon examination that is associated with urinary tract or sexual dysfunction symptoms.
- Epididymal pain syndrome is the experience of persistent or recurrent episodic pain located in the epididymis upon examination that is associated with urinary tract or sexual dysfunction symptoms.
- Post-vasectomy pain syndrome is a scrotal pain syndrome that follows vasectomy.

#### Evidence Acquisition

A literature search was conducted using Google and the National Library of Medicine's PubMed databases to identify published hard copy or electronic original articles and review

articles on testicular pain, up to March 2020. The search terms included: MeSH terms: testicular disease (classification, complications, etiology, trauma, microbiology, pathology, pathophysiology, secondary, surgery, and therapy) and vasectomy; Non-MeSH terms: acute and chronic orchialgia, scrotalgia, orchidynia, groin pain, epididymalgia, testalgia, chronic testicular pain (CTP), chronic scrotal pain syndrome (CSPS), testicular pain syndrome, epididymal pain syndrome, and post-vasectomy pain syndrome. The reference list of the articles retrieved, as well as relevant reviews and cases report, were also evaluated. The initial search produced 615 articles, and after applying additional filters, 143 studies were included in the present review.

#### Causes of Testicular Pain

For better understanding, we recommend dividing the causes of acute and chronic testicular pain into ten subgroups, according to the etiology of the pain:

- Subgroup 1:** Infectious causes (acute and chronic).
- Subgroup 2:** Tumoral causes (acute and chronic).
- Subgroup 3:** Traumatic and postoperative causes (acute and chronic).
- Subgroup 4:** Torsional causes (acute and chronic).
- Subgroup 5:** Vascular causes (acute and chronic).
- Subgroup 6:** Immunologic causes (acute and chronic).
- Subgroup 7:** Neurologic causes (acute and chronic).

**Subgroup 8:** Pharmacologic causes (acute and chronic).

**Subgroup 9:** Obstructive causes (acute and chronic).

**Subgroup 10:** Miscellaneous causes (acute and chronic).

*Subgroup 1: Infectious causes*

Throughout history, differentiating a surgical emergency, such as torsion, from a medical emergency, such as epididymitis, has been important. In 1934, at the St. Albans Naval Hospital in New York, Donald Prehn made an interesting observation: testicular pain in sailors caused by gonococcus was alleviated by elevating the affected testicle, but testicular pain due to torsion worsened with elevation, ergo, the origin of the classic Prehn sign.<sup>(16)</sup> Epididymitis and epididymo-orchitis are the most frequent causes of acute pain in all ages, except for prepubescent boys, in whom there are fewer incidences of acute epididymitis.

Infectious etiologies are mostly bacterial, viral, mycobacterial, fungal, or sterile inflammation of the epididymis that only appears in children. In children, the most frequent cause of orchitis, with severe testicular pain but no epididymitis, is infection due to the mumps virus, also called *infectia urliana*. The clinical significance of acute inflammation seen in that scenario can be important, given that it can cause an authentic compartment syndrome of the testicular pulp, with a subsequent high risk of testicular atrophy. Persistence of infectious agents or certain types of microbes can cause chronic infections. Such infectious agents include brucellar epididymo-orchitis,<sup>(17)</sup> deep mycosis (e.g., actinomycosis, histoplasmosis,

coccidioidomycosis, and echinococcosis), testicular leprosy (pain appeared in 68% of patients and testicular compromise was more frequent in the lepromatous variety (62%) than in the dimorphic variety (30%), testicular paludism (*falciparum*), genital tuberculous with suppurative changes and fistulas in the scrotal skin, schistosomiasis or filarial orchitis (produced by *Loa-loa* microfilaria, and is usually unilateral),<sup>(18)</sup> granulomatous orchitis, and syphilitic orchitis (*T. pallidum*).

A testicular abscess is a complication of bacterial epididymo-orchitis in adults, or an undiagnosed torsion, trauma, or systemic infection, such as scarlet fever, influenza, and typhoid fever, in children. Fournier's gangrene, or spontaneous gangrene, is a necrotizing infection with direct involvement of or secondary extension to the scrotum. It is a relatively painless condition because the fasciitis destroys the nerve terminals of the skin. Testicular malakoplakia is seen in advanced-age patients. It is characterized by a painful increase in testicular size and is diagnosed solely through biopsy, through which the Michaelis-Gutmann bodies can be seen. Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a common disorder in which the two main clinical features are pelvic pain and lower urinary tract symptoms. Finally, chronic testicular pain may be a component of urologic chronic pelvic pain syndrome (UC-PPS), previously considered NIH Category 3 prostatitis or CPPS, which correctly implies that the symptoms are neither due to an infectious etiology or an abnormality of the prostate gland. There is growing evidence to support several non-urologic causes, such as myofascial trigger points, with well recognized referred pain patterns (often including the scrotum or testes) and functional somatic syndromes. Functional

somatic syndromes encompass an enigmatic constellation of pain syndromes that are associated with testicular pain, penile pain, painful ejaculation, and reduced sexual function.<sup>(19-21)</sup>

#### *Subgroup 2: Tumoral causes*

Tumor-derived testicular pain is rarely acute. There is an old medical aphorism that says, "when there is a major injury after a minor trauma, a tumor must be ruled out". During the examination, painful, enlarged testes can be confused with an epididymo-orchitis or testicular torsion. Aside from the classic seminomatous and non-seminomatous germ cell tumors, other diseases less commonly involving neoplasms of the testis must be considered, such as lymphomas or leukemia, which may encapsulate the cord or glans penis. That situation occurs more frequently in children or young adults. Chronic orchialgia, in the context of a testicular tumor, is not rare in underdeveloped countries, where healthcare systems do not routinely provide screening and its consequently early diagnosis of testicular cancer in young men. In a culture where preventive healthcare does not exist, it is not uncommon for men to suffer from chronic testicular pain caused by the delayed diagnosis of testicular tumors. The extramedullary, generally bilateral, testicular presentation of multiple myeloma is rare, but possible, and finally, sarcoidosis can infiltrate the testis, producing chronic pain.<sup>(22,23)</sup>

#### *Subgroup 3: Traumatic causes*

Trauma must be considered in all ages as the cause of acute pain. Severity varies from simple

organ contusions to testicular rupture (a force of 50 kg is required to tear or break the tunica albuginea). Traumatic epididymitis is a cause of pain, but there are other injuries that aggravate pain, such as hematoceles or intratesticular hematomas, tears of the albuginea, laceration of testis, or fractures. Self-palpation orchitis, a less serious condition, may be suspected in patients that manipulate their own scrotum to achieve a sensation of pleasure or among patients that compulsively perform self-examinations, looking for cancer. Acute, subacute, or chronic testicular pain can be triggered after any surgery on the genital area or the scrotum, such as herniorrhaphy, varicocelectomy (injury or entrapment of nerve branches, passive congestion of the epididymis and/or testis by the sudden diminution of the venous return), spermatocelectomy, orchidopexy (complete or partial), needle biopsy of the testis, or semen aspiration for infertility procedures, laparoscopic donor nephrectomy (can produce ipsilateral orchialgia in 9.6% of men) through various mechanisms, including the surgical wound, nerve branch injury, inadequate healing, edema, and other complications specifically derived from each of the different procedures. Testicular or scrotal pain is more often noticed after laparoscopic inguinal hernia repair than after the open procedure. Pain following vasectomy has been reported in 33-56% of patients. The syndrome is generally recognized as post-vasectomy pain syndrome (PVPS), but genuine post-vasectomy pain syndrome (PVPS) is postoperatively diagnosed in 10% of patients and is also known as post-vasectomy orchialgia or late post-vasectomy syndrome. There are a number of theories that explain post-vasectomy pain syndrome: Epididymal congestion, painful spermatic granuloma, nerve entrapment during healing,

ejaculatory derangement, or post-vasectomy depression (1%). Epididymitis nodosa is a delayed complication after a vasectomy, requiring additional repair after the rupture of ducts due to increased pressure caused by the surgery.

Finally, the uncommon, but more severe dislocation of the testis is a result of trauma and produces damage or avulsion of the fascia surrounding the testis and/or of the gubernaculum testis. Dislocation is severe in an area whose radius is the length of the spermatic cord. The following rupture locations have been 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%).<sup>(15,24-30)</sup>

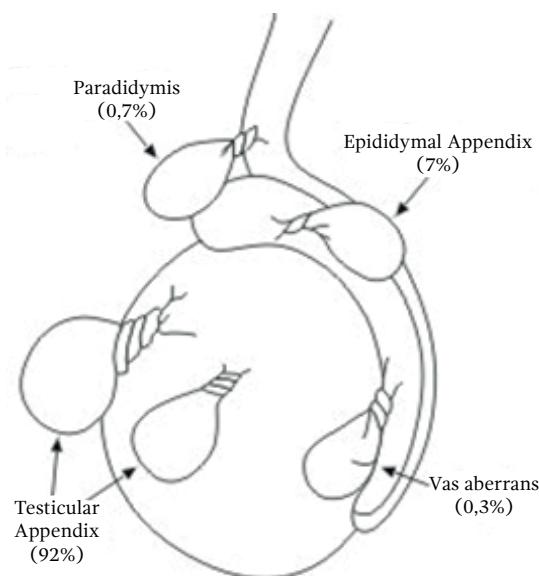
#### *Subgroup 4: Torsional causes*

Testicular torsion presents in two forms: intravaginal and extravaginal. The intravaginal abnormality is the less frequent and presents in newborns up to 15 months, with 72% of cases occurring in the womb. The extravaginal abnormality known as “bell clapper deformity” is commonly seen in emergency services. Inadequate attachment of the tunica vaginalis over the spermatic cord allows the testis to turn freely on its axis. Intermittent testicular torsion (ITT) should also be considered among the torsional causes. Patients that had an episode of acute testicular torsion were reported to have had a previous history of intermittent pain that spontaneously resolved. In most cases of ITT, there is an episode of torsion with spontaneous detorsion.<sup>(31)</sup>

The differential diagnosis in acute testicular pain, with or without inflammation, inclu-

des testicular appendage torsion. It is generally unilateral, but cases of synchronous torsion have been described. Presentation is more frequent between 7 and 12 years of age. The patient with twisted testicular appendages can have a previous history of intermittent pain, even for months. During examination, there is often extreme sensitivity in the superior portion of the testis and the clinical manifestation is complete with the appearance in the scrotum of the pathognomonic “blue dot sign”. Four intrascrotal appendages can become twisted: the testicular appendage or hydatid of Morgagni is a remnant of Mullerian ducts and is responsible for 92% of torsions; an appendage of the head of the epididymis or Haller’s organ is a Wolffian remnant and contributes to 7% of torsions; Giralde’s organ, also called the paradidymis or innominate body, another Wolffian remnant, accounts for 0.7% of cases; and vas aberrans, a mesonephric remnant, located at the junction of the body and tail of the epididymis, with a 0.3% occurrence (Figure 1).<sup>(32)</sup>

**Figure 1**



#### *Subgroup 5: Vascular causes*

Aneurisms of the abdominal aorta, iliac artery, or testicular arteries can initially start as a painful problem. Aortic dissection is also an unusual presentation of severe testicular pain. Henoch-Schoenlein purpura (HSP) is systemic acute vasculitis and its nonrenal genitourinary presentation can include scrotal pain and swelling.<sup>(33)</sup> Testicular vasculitis is part of a systemic condition of an autoimmune disease, such as polyarteritis nodosa, which compromises the medium and small arteries of the testis, or more rarely, Goodpasture syndrome.<sup>(34)</sup> Varicocele is the cause of acute or chronic testicular pain. Painful varicocele varies from the sensation of weight and annoyance to frank orchialgia.

The mechanisms of pain are venous stasis, incompetent valves, and the force of gravity when a person stands upright, which increases testicular congestion.<sup>(35)</sup> Thrombophlebitis of the pampiniform plexus, which is usually unilateral, is an acute condition with intense pain that resembles torsion of the testis or the testicular appendages.<sup>(36)</sup> Splenosis is the dissemination of splenic tissue that can reach up to the inguinal region and cause severe testicular pain that is only alleviated by the removal of the ectopic tissue. Testicular hemangioma is an uncommon and benign condition, with an intratesticular arteriovenous malformation that can be a source of pain. Finally, testicular infarction is usually segmental, and it is secondary to other pathologies with inflammation and pain. Initial onset can be similar to that of testicular torsion, with a sudden and lacerating pain, but it is also described in patients with falciform anemia or septic embolus during bacterial endocarditis.<sup>(37)</sup>

#### *Subgroup 6: Immunologic causes*

Some immune diseases are potential causes of testicular pain. Autoimmune orchitis is characterized by testicular inflammation and the presence of specific antisperm antibodies (ASAs). Primary autoimmune orchitis is defined by infertility and asymptomatic orchitis, associated with ASA use (100%) and no systemic disease, whereas secondary autoimmune orchitis is characterized by symptomatic orchitis and/or testicular vasculitis associated with a systemic autoimmune disease. Sweet's syndrome is acute febrile neutrophilic dermatosis, with a history of recurrent fever, noncontagious mouth ulcers (aphthae), phlebitis, pneumonitis, arthritis, and orchitis with chronic pain. Acute idiopathic scrotal edema is a self-limited condition that is usually painless. However, sometimes it is very dramatic and confusing due to the edema and must be considered in the differential diagnosis of other pathologies. The process is considered idiopathic, but insect bites, allergy, chemical dermatitis, or trauma can be possible causes.<sup>(38-40)</sup>

#### *Subgroup 7: Neurologic causes*

The diseases included in the neurologic subgroup cause pain through direct or indirect irritation of the nerves. Cremasteric muscle spasms with synkinesis cause significant pain and limit physical activity. Lumbar synchondrosis, or primary cartilaginous transition joints between the thoracic and lumbar vertebrae (T12-L1) or the lumbosacral joint (L5-S1), is a cause of chronic orchialgia. Pudendal channel syndrome with pudendal nerve entrapment gives rise to neuropathy with chronic pain in

the prostate, scrotum, and rectum. It is caused by the compression of the nerve in the subluxation of the levator ani muscle. Adductor tendonitis, gluteal fibrosis, or psoas muscle spasm are potential causes of referred naturopathic scrotal pain.

Phantom orchialgia is secondary to radiculitis through irritation of the nerve roots between T10 and L1. A herniated lumbar disk produces paroxysmal, radicular pain that is usually subacute upon onset and then becomes chronic. Diabetic neuropathy is a frequent cause of chronic testicular pain. Abdominal epilepsy, or cerebral dysrhythmia, causes acute paroxysmal testicular or abdominal pain as the main manifestation. Finally, koro-like syndrome is a psychiatric condition that presents with anxiety and fear of death, along with genital retraction. A variant of that syndrome includes symptoms of intense episodic scrotal pain, with panic attacks.<sup>(41,42)</sup>

#### *Subgroup 8: Pharmacologic causes*

The mechanism of pharmacologic pain is variable. For example, epididymitis is associated with visceral pain, but it can also be neuropathic or chemical. Mazindol is a sympathomimetic amine that stimulates the central nervous system and is used as an anorectic.<sup>(43)</sup> Amiodarone is a class III antiarrhythmic that blocks the sodium channels (with a high affinity for open and inactivated sodium channels) and potassium channels, causing chemical epididymitis and testicular pain. That condition has been described in up to 11% of adult patients. Desipramine is a tricyclic antidepressant (TCA) that inhibits the reuptake of norepinephrine. It particularly produces postcoital testicular

pain and painful retraction during intercourse. Gadopentetate dimeglumine (Gadolinium) is used as an intravenous radiocontrast agent to enhance images in nuclear magnetic resonance imaging,<sup>(44)</sup> and its fast intravenous injection has been reported to cause testicular pain. The withdrawal of imipramine has also been reported to cause testicular angina.<sup>(44)</sup> Vitamin B12 deficiency has recently been accepted as a cause of chronic orchialgia.<sup>(45)</sup>

#### *Subgroup 9: Obstructive causes*

A group of pathologies with symptoms of ureteral obstruction, such as stones, uretero-pelvic junction stricture, retrocaval ureter, retroperitoneal fibrosis, constipation, and hydronephrosis, produces referred pain to the testis when a nerve is being irritated by intimate contact of the ureter with the genitofemoral nerve at the L4 spinal level.<sup>(46)</sup> In abdominal tumors and cirrhosis, testicular pain can develop due to secondary varicocele. The descending colon, distended with fecal material, and the nutcracker phenomenon of the left renal vein between the superior mesenteric artery and the aorta can produce transitory obstructions of the left testicular vein with episodes of pain. The nutcracker phenomenon can also lead to hematuria.

Another group of pathologies produces pain due to testicular congestion. In simple hydrocele, spermatic cord orchialgia is reported when there is underlying inflammation of the testis or epididymis, tension hydrocele, or when hydrocele is secondary to complicated conditions such as trauma, bleeding, or infection. An epididymal cyst (spermatocele) contains nonviable semen and is a cause of chronic pain,

as a result of inflammatory cytokines. Cystic degeneration, or testicular microlithiasis, can cause chronic orchialgia through different mechanisms. Pelvic congestion in adolescents that are not sexually active and have nocturnal emissions is commonly known (in Colombia) as “fiancé colic”. There are variations in which a combination of factors produces microtraumas that result in pain that is not resolved through sexual activity. Macroorchidism is a disorder in which testicular volume increases to more than 25 cc, as occurs in fragile X syndrome and Atkin-Flaitz syndrome. Patients usually have mental retardation and a marfanoid phenotype.

Other pathology groups present with intratesticular obstruction and/or deposit of substances and testicular pain. Hyperuricemia is a deposit of uric acid crystals in the tubules of the epididymis that cause pain. Tubular ectasia of the rete testis (TERT) is a benign cystic condition of the testis that is mostly seen in men over 55 years of age.<sup>(47)</sup> Ultrasound imaging reveals an intratesticular area containing an abundance of tight and anechoic (cystic) lesions. Constrictive albuginitis causes chronic pain due to fibrosis of the peritubular tissues with a heavy, yellowish, and rigid testicular albuginea that shows an excess of hyalinosis and fibrosis.

#### *Subgroup 10. Miscellaneous causes*

In appendicitis, the initial manifestation can appear as acute testicular pain on the right side. In hemodialysis, an unusual manifestation of painful testicular ischemia was reported. Testicular pain can also result from indirect inguinal and femoral hernias with intra-abdominal content. Its clinical manifestation can be similar to

that of acute scrotum, whose symptoms vary from painless masses to painful swollen masses. Retractile testis produces testicular pain when patients feel the testis pulled toward the scrotum. Finally, idiopathic scrotal fat necrosis is another unusual cause of testicular pain. It is characterized by necrosis of the intrascrotal fat, adjacent to the perineum and is typically present in prepubertal boys, but not in adults.<sup>(48-50)</sup>

## **Treatments**

“While chronic orchialgia may appear to be an insoluble puzzle, the condition can be managed in an algorithmic fashion”. The objective is to quickly define whether treatment should be carried out by the urologist or by a pain management specialist. In addition, treatment must be gradual (e.g., blockade of the spermatic cord before surgery) and the specific causes corrected (e.g., varicocele or hernia).

#### *Pharmacologic treatment options:*

- Common nonopiod analgesics (paracetamol or acetaminophen) are the first step of therapeutic management.
- Nonsteroidal anti-inflammatory drugs are the second step.
- Opioid analgesics have been considered more useful for inflammatory problems than for neuropathic pain.
- Antimicrobials, according to the site of infection and the isolated germ.
- Anticonvulsants or neuroleptics, such as gabapentin, pregabalin, and carbamazepine, have been useful in alleviating hyperalgesia and allodynia, which are classic cha-

characteristics of neuropathic pain.

- $\alpha$ -adrenergic antagonists: alfuzosin, terazosin, doxazosin, silodosin, or tamsulosin.<sup>(51)</sup>
- Tricyclic antidepressants: several reports with amitriptyline have indicated symptom improvement.<sup>(15)</sup>
- Other antidepressants, such as duloxetine, selective serotonin, and norepinephrine reuptake inhibitors.<sup>(52)</sup>
- Allopurinol in hyperuricemia associated with testicular pain.
- Vitamin B 12 in cases of deficiency.
- Analgesia through CB1 cannabinoid receptors, located in the area of the spinal cord associated with nociception and calcium flow regulation.<sup>(53)</sup> Although it has not been used in testicular pain, its mechanism appears promising.<sup>(54)</sup>
- Botulinum toxin A in the bilateral cremasteric muscles in patients with intractable spasm has also been used with hopeful results.<sup>(55)</sup>
- Drugs delivered by nanotechnology: the future of testicular therapy.

#### *Non-pharmacologic treatment options*

##### *Noninvasive alternatives*

- Pain education: It is always valuable to include education about the causes of pain, which includes addressing the anxieties that patients with pathology of unknown etiology have. Information improves treatment adherence.<sup>(15)</sup>
- Restricted physical activity is a complementary treatment option, especially in cases of pain that originates in acute inflammatory scenarios.

- Psychotherapy or cognitive behavioral therapies can attenuate or improve cases of patients with chronic testicular pain.
- Perineal or pelvic floor massage and the release of myofascial trigger points in the perineum or pelvis.
- Transcutaneous electrical nerve stimulation (TENS) stimulates certain nerve fibers to block pain transmission at the central level.<sup>(56)</sup>
- Pulsed radiofrequency.
- Biofeedback therapy.<sup>(57)</sup>

##### *Minimally invasive options*

- Local anesthetic infiltration of the spermatic cord, with or without steroids.
- Local anesthetic infiltration of the pelvic plexus, under TRUS guidance. A mixture of lidocaine and steroids can alleviate testicular pain.
- Needle aspiration of epididymal cyst.
- Direct intraprostatic injection of an antibiotic, anesthetic, or steroid is a therapeutic option to direct pelvic plexus injection.
- Injectable dehydrated amniotic/chorionic membrane allograft (AmnioFix®), a substance derived from human amniotic membrane, has been shown to reduce scar tissue formation.<sup>(58)</sup>
- Acupuncture and electroacupuncture have been used by practitioners of traditional Chinese medicine for more than 2000 years. Their effects may be mediated by neuromodulation to inhibit pain transmission, as well as normalize the function of various midbrain nuclei.<sup>(59)</sup>

### Surgical treatment options

- Microsurgical spermatic cord denervation (MSCD) with open, laparoscopic, or robotic-assisted approaches have been described.<sup>(60)</sup>
- Pulsed radiofrequency (PRF) denervation of the spermatic cord.<sup>(61)</sup>
- Ultrasound-guided targeted microcryoablation (UTM).
- Denervation or neurectomy of the ilioinguinal, iliohypogastric, or genitofemoral nerves to improve chronic pain.
- Denervation of the spermatic cord, or cord stripping, is described in post-vasectomy syndrome because exclusive eradication of sympathetic innervations can eliminate the sympathetic dystrophy reflex.
- Spermatic granuloma excision, vasovasostomy or vasoepididymostomy, in post-vasectomy pain syndrome (PVPS).
- Decompression for pudendal nerve entrapment.
- Epididymectomy is a procedure with contradictory results. It is used in post-vasectomy persistent chronic pain, with enlargement of the epidididymis.<sup>(62)</sup>

- Varicocelectomy, hydrocelectomy, inguinal hernia repair, spermatocelectomy, and orchidopexy have been used as treatment for patients with the corresponding diagnoses.
- Orchectomy is a “last resort” procedure for eliminating neuropathic pain, but it also has potential risks, including failure to eradicate the pain.<sup>(63)</sup>

### Conclusion

Testicular pain is a vast field, in which multiple organs and systems interact. It has numerous possible etiologies that include genitourinary and non-genitourinary conditions. Clearly, when there are many diagnostic and therapeutic options in a clinical situation, only trials and training will result in the proper understanding of chronic pain of the testicle as part of a complex pain syndrome with an enigmatic origin, its own biochemical cascades, singular pathways, and an unusual variety of signs and symptoms. Given that common analgesics, and even opiates, fail in the management of testicular pain, the urologist must have a comprehensive understanding of the patient’s clinical scenario and appropriately select treatment from the wide range of therapeutic options.

**Table 1. Testicular pain etiology**

	ACUTE PAIN	CHRONIC PAIN
INFECTIOUS	Epididymitis and/or acute orchitis	Chronic epididymitis (brucellar, deep mycosis, leprosy, paludism, TBC, syphilis)
	Mumps orchitis	Testicular malakoplakia
	Testicular abscess	Chronic prostatitis
	Fournier’s gangrene	

Continúa...

	ACUTE PAIN	CHRONIC PAIN
TUMORAL	Seminoma	Seminoma
	Choriocarcinoma	Choriocarcinoma
	Lymphomas	Lymphomas
	Leukemias	Leukemias
TRAUMATIC AND POSTOPERATIVE	Acute trauma	Post-vasectomy pain syndrome (PVPS)
	Dislocation of testis	Epididymitis nodosa
		“Self-palpation” orchitis
		Post-herniorrhaphy
		Post-varicocelectomy
		Post-spermatocelectomy
		Post-laparoscopic donor nephrectomy
TORSIONAL	Torsion of the testis (extravaginal and intravaginal)	Intermittent testicular torsion
	Perinatal torsion of the spermatic cord	
	Torsion of appendix	
VASCULAR AND IMMUNOLOGIC	Aneurysms	Varicocele
	Henoch-Schonlein purpura	Sweet’s syndrome
	Testicular vasculitis	Intratesticular arteriovenous malformation
	Acute idiopathic scrotal edema	Splenosis
	Autoimmune orchitis	
	Thrombophlebitis of the pampiniform plexus	
	Testicular infarction	
NEUROLOGIC AND MUSCULOSKELETAL	Tendonitis of the inguinal ligament	Synchondrosis
	Adductor tendinitis	Pudendal nerve entrapment
	Psoas spasm	Gluteal fibrosis
	Abdominal epilepsy	Phantom orchialgia
		Lumbosacral radiculopathy pain
		Koro’s syndrome
		Diabetic neuropathy
		Pelvic floor tension myalgia

Continúa...

	ACUTE PAIN	CHRONIC PAIN
PHARMACOLOGIC	Mazindol	Mazindol
	Amiodarone	Amiodarone
	Desipramine	Desipramine
	Gadopentetate dimeglumine ( <i>Gadolinium</i> )	Gadopentetate dimeglumine ( <i>Gadolinium</i> )
	Imipramine withdrawal	Imipramine withdrawal
		Vitamin B12 deficiency
MISCELLANEOUS	Pelvic congestion	Inguinal and femoral hernias
	Appendicitis	Retractile testis
	Meconium periorchitis or vaginalitis	Simple or communicating hydrocele
	Ureteral stones	Epididymal cyst (spermatoceles)
	Ureteropelvic obstruction	Hyperuricemia
	Retrocaval ureter	Macroorchidism
	Retroperitoneal fibrosis	Testicular microlithiasis
	Hydronephrosis	Constrictive albuginitis
	Hemodialysis	Multiple myeloma
	Constipation	Sarcoidosis
	Idiopathic scrotal fat necrosis	Cirrhosis

## Acknowledgements

The authors wish to thank Jeannette Potts MD, Vista Urology & Pelvic Pain Partners ([www.drjeannettepotts.com](http://www.drjeannettepotts.com)) for her help in reviewing and editing this manuscript.

## Conflict of interest

The authors declare no conflict of interest.

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