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**Invited Review**

# Infection, inflammation, and sexual function in male and female patients—recommendations from the Fifth International Consultation on Sexual Medicine (ICSM 2024)

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## Abstract

**Introduction:** Sexual dysfunction in men and women is an important clinical issue; infection and inflammation can cause social, medical, and psychological problems that have a profound impact on sexual and reproductive health worldwide.

**Objectives:** We set out to identify sexual dysfunctions in men and women that arise from infection and inflammation and propose meaningful interventions, as evaluated by the Fifth International Consultation on Sexual Medicine (ICSM) held in June 2024 in Madrid (Spain).

**Methods:** We searched MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) for published peer-reviewed journal articles and ClinicalTrials.gov and the World Health Organization's (WHO's) International Clinical Trials Registry Platform for prospective trials. This manuscript represents the opinions of 10 experts from 6 countries developed in a consensus process after completing the literature review, which produced a list of recommendations graded as weak or strong. This document was presented for peer review and debate in a public forum, and revisions were made based on the recommendations of chairpersons of the 5th ICSM.

**Results:** Infections, and in particular sexually transmitted infections (STIs), dramatically affect the sexual and reproductive health of individuals and couples, irrespective of sexual orientation and gender. Similarly, non-communicable chronic diseases (NCDs), through the common pathogenetic mechanism of inflammation, can directly impair the ability to copulate, reproduce, and enjoy sexual life.

**Conclusions:** This expert consensus recommends prioritizing early detection, comprehensive treatment approaches, and preventive measures to mitigate the effects of infection and inflammation on sexual health, both for the patient and the couple. These insights provide a foundation for improving patient outcomes and fostering global awareness of the interconnections between infection, inflammation, and sexual dysfunction.

**Keywords:** sexual dysfunction; chronic inflammation; NCD infection; STD; chronic pelvic pain—COVID-19.

## Introduction

Systems medicine is an interdisciplinary part of medicine that looks at the systems of the human body as part of an integrated whole, considering biochemical, physiological, and environmental interactions. Systems medicine studies the complex interactions within the human body in light of a patient's genomics, behavior, and environment.[1] Typically, systems medicine studies the 2 prominent families of diseases impairing human survival, health, and wellbeing: communicable (infectious) and non-communicable diseases (NCDs), which can be acute or chronic. Interestingly, both are connected to lifestyle, and both are so directly linked to sexual and reproductive health, such that the equation SM = SM (systems medicine equals sexual medicine) has been postulated.[2]

Another strong support for the equation is the common mechanism of action. Inflammation, in its acute, subacute, and chronic expression, is the major pathogenetic milieu for both NCDs and sexual dysfunction. However, inflammation is also the effect, as well as a risk factor, for communicable diseases, such as infectious diseases, which can both affect sexual life and be a direct consequence of sexual life (Figure 1).

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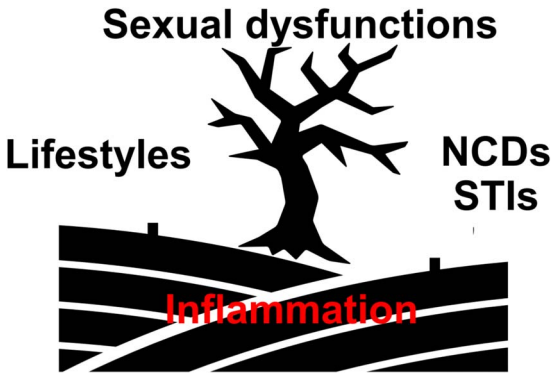


**Figure 1.** The mechanism producing health and diseases. The sterile tree producing non-communicable chronic diseases (NCDs) and sexually transmitted infections (STIs) grows nourished by suboptimal lifestyle choices in the poisoned grass of inflammation, having sexual dysfunction as an early toxic fruit.

This is a major reason to collectively discuss diseases that may seem not connected but share the common ability to reduce not only overall health but also sexual health. A typical paradigmatic representation of the link between infections and inflammation is COVID-19; it is an acute respiratory viral disease, but it can also produce chronic sequelae (long COVID). Moreover, the risk of COVID-19 infection, its chronic sequelae, and its lethal consequences are influenced by comorbidity with numerous NCDs, which, in turn, are exacerbated or perpetuated by suboptimal lifestyles. The link between COVID and NCDs is the presence of inflammation at several tissue sites, particularly the endothelium, the principal peripheral actor of the human sexual response. Knowing that endothelial health is heavily influenced by lifestyle, this establishes a self-perpetuating relationship.

For all these reasons, sexual dysfunctions have been considered an early signal of NCDs as a "canary in the coal mine."[3] Presented herein are recommendations of 10 experts in the field following an extensive literature review and consensus process that graded the available evidence, which was presented at the 5th International Consultation on Sexual Medicine (ICSM). We discuss both infectious and inflammatory diseases that can negatively impact sexual function in men and women with 29 recommendations for reducing their morbidity regarding sexual function.

## Methods

We searched MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) for published peer-reviewed journal articles and ClinicalTrials.gov and the World Health Organization's (WHO's) International Clinical Trials Registry Platform for prospective trials. Our expert opinion (produced by 10 experts from 6 countries and developed in a consensus process) was based on grading evidence-based medical literature. A modified Delphi method was used for making recommendations.[4]

## Results

Based on the retrieved articles, a total of 29 recommendations (Table 1) to aid clinical decision-making were produced (Table 1). Key details are included and discussed herein.

### Male and female sexually transmitted infection and sexual dysfunction

Sexual dysfunction in men and women is clinically significant, and sexually transmitted infections (STIs) have a profound impact on sexual and reproductive health worldwide, which can be accompanied by social and psychological problems. More than 1 million STIs are acquired every day.[5] Sexually transmitted infections are generally acquired and transmitted through sexual contact, including through bodily fluids or skin contact via vaginal, oral, or anal sex, with different degrees of risk, as shown in Table 2. Sexually transmitted infections are a major health problem that disproportionately affects young people, although senior populations are currently at increasing risk.[6] Sexually transmitted infections are prevalent not only in developing but also in developed countries, causing a plethora of diseases, such as pelvic inflammatory disease, ectopic pregnancy, infertility, chronic pelvic pain, genital lesions, genital neoplasms, adverse pregnancy outcomes, immune system dysfunction, liver disease, and even death.[7,8]

Approximately 1 in 5 adults in the United States acquired an STI in 2018, with a key factor in the spread of these infections being their varied clinical presentation, which includes urogenital, pharyngeal, and rectal involvement as well as a large number of asymptomatic cases. Approximately 70% of infections with HSV and trichomoniasis and 53%-100% of extragenital gonorrhea and chlamydia infections are asymptomatic or associated with few symptoms.[9]

In 2020, the World Health Organization (WHO) estimated there were 374 million new infections with 1 of the 4 major STIs: chlamydia (129 million), gonorrhea (82 million), syphilis (7.1 million), or trichomoniasis (156 million).[5] More than 490 million people were estimated to be living with genital herpes in 2016, and an estimated 300 million women have a human papillomavirus (HPV) infection, the primary cause of cervical cancer in women and anal cancer among men who have sex with men. An estimated 296 million people are living with chronic hepatitis B, globally.[7]

The main STIs that present an important impact on sexual function include chlamydia, gonorrhea, syphilis, trichomoniasis, hepatitis B virus (HBV), herpes, human immunodeficiency virus (HIV), and HPV. COVID-19, although not specifically an STI, is also listed among these infections.

Each infection will be introduced by a paragraph devoted to briefly describing its epidemiology, clinical presentation, diagnosis, and impact on sexual function. Indications regarding treatment are provided in Table 3.

#### *Chlamydia, gonorrhea, and trichomonas*

Urogenital chlamydial infection, caused by *Chlamydia trachomatis*, is the most common bacterial STI, and approximately 131 million new cases occur globally every year.[13] *C. trachomatis* infection is asymptomatic in more than 50% of cases.[14] However, non-gonococcal urethritis can manifest with urethral discharge, burning with micturition, penile tip irritation, and watery, viscous excretion ("morning milker"). Pelvic infection can lead to pelvic inflammatory disease (PID) and subsequent adhesion development, a possible risk factor for tubal infertility.

In 2021, more than 710 000 cases of *Neisseria gonorrhoeae* (Gonorrhea) infection, a species of Gram-negative diplococci bacteria, were reported in the United States, making it the

**Table 1.** List of recommendations from the "Infection, Inflammation and Sexual Function in Male and Female Patients" Committee—Fifth International Consultation on Sexual Medicine (ICSM 2024).

**Recommendation #1:** It is imperative to pay attention to the consequences that sexually transmitted infections (STIs) may have on the sexuality of affected patients and their partners (***strong***). Partners of STI-infected patients should be screened and treated (***strong***).
**Recommendation #2:** We recommend paying particular attention to the sexual consequences of chlamydia, gonorrhea, and trichomonas infection. In men, they can be associated with an increased risk of epididymitis, prostatitis, and decreased sperm motility. In women, they are a common cause of vaginal discharge, and they are associated with poor birth outcomes and an increased risk of pelvic inflammatory disease (PID) and pelvic adhesions (***strong***).
**Recommendation #3:** In settings with high hepatitis B surface antigen seroprevalence in the general population (defined as >2% or > 5% HBsAg seroprevalence), we recommend that all adults have access to and be offered HBsAg testing with referral to prevention, care, and treatment services (***weak***). While there is currently no specific treatment for acute hepatitis B, chronic hepatitis B can be treated with antivirals, including tenofovir or entecavir, while the disease is preventable with a vaccine (***weak***).
**Recommendation #4:** We recommend prompt DAA treatment in the case of hepatitis C (HCV) infection, HCV screening and prevention strategies including using condoms, reduced-risk sexual practices, infection prevention strategies, and sexual education (***strong***).
**Recommendation #5:** We recommend paying attention to the unique impact that HIV has on the sexual health of men and women affected (***strong***). We recommend prompt and thorough treatment of infection (***strong***) and infection prevention strategies (eg, condom usage, dental dams, use of clean needles for intravenous drug use, and reduced-risk sexual practices) (***strong***). Psychotherapy can also help these individuals to resume their sexual activities safely (***strong***).
**Recommendation #6:** We suggest that for the detection of HPV in men, the anatomic location is important. There because there is considerable variability in the incidence of HPV depending on the location (penile body, glans, foreskin, coronal sulcus) (***weak***). Samples from the urethra and semen have less positivity for the detection of HPV (***weak***). Vaccination programs have presented high effectiveness in preventing HPV infection and HPV-related lesions (***weak***).
**Recommendation #7:** We recommend treating infections affecting male and female reproductive organs, considering they have far-reaching consequences for sexual function, both in the individual and in the couple (***strong***). It is imperative to address not only the infection itself but also any associated pelvic floor dysfunction, sexual dysfunction, and mental health issues to provide comprehensive care. Sexual education is a key factor in STI prevention of STI (***strong***). By understanding the complex interplay between infections and sexual health, healthcare professionals can optimize treatment strategies and improve patient outcomes.
**Recommendation #8:** We recommend that the use of facial masks (***strong***), as well as sexual protection such as condoms and dental dams (***weak***) during oral sex, could be appropriate interventions to prevent transmission. Further studies are necessary to determine rates of SARS-CoV-2 transmission during specific sexual activities, such as anilingus (oral–anal contact) and insertive anal sex. Hence, we suggest that specific protection in these settings may not be needed for COVID-19 prevention (***weak***). Urine, vaginal secretions, and semen are highly unlikely to transmit COVID-19. Thus, we suggest that specific protection is not required for COVID-19 prevention, while we recommend adherence to reduced-risk sexual practices to prevent other STIs (***weak***).
**Recommendation #9:** We recommend that special attention should be paid to sexual health in COVID-19-affected men, since erectile dysfunction (ED) can represent either a short-term or a long-term complication of COVID-19 (***strong***). Given that COVID-19 might act as a potential initiating trigger for the onset of erectile impairment, or an aggravating factor for its progression to more severe forms, we suggest that subjects with a sudden onset or worsening of ED might also consider precautionary quarantine or nasopharyngeal swab (***weak***).
**Recommendation #10:** COVID-19 is associated with short-term sperm and testosterone impairment, whereas long-term consequences have still not been sufficiently clarified. We suggest that testicular function, including T and sperm concentrations, should be monitored in patients who have recovered from SARS-CoV-2 (***strong***). We can confirm COVID-19 vaccination does not negatively impact sperm parameters (***strong***).
**Recommendation #11:** Given the psychological impact of lockdowns, social isolation, and pandemic-related stress on individuals' sexual wellbeing, we recommend efforts for preventive strategies be concentrated between pandemics, to reduce the negative impact of these factors (***strong***). We recommend, during health emergencies that we prioritize sexual health, as it is deeply connected to overall wellness, and to provide recommendations on how to maintain sexual wellbeing while minimizing the risk of contamination (***strong***).
**Recommendation #12:** Given the existing challenges and health disparities faced by the LGBTQ+ community, there is reason to suspect that such a burden is exacerbated during periods of lockdown and social distancing. We recommend implementing targeted sexual and mental health interventions that specifically address the needs of the LGBTQ+ community, including HIV care, gender-affirming treatments, and mental health services (***strong***).
**Recommendation #13:** We suggest that sexual long COVID (SLC) might become the clinical biomarker of the underlying complications of long COVID, as patients who develop symptoms of SLC may have worse risk profiles regarding long-term consequences of COVID-19 (***strong***). We also suggest that for women who have experienced COVID-19 to consider the possible repercussions on sexual health. We encourage proactively discussing sexual function and offering resources (***strong***).
**Recommendation #14:** Sexual dysfunction, like erectile and ejaculatory disturbances in men, and reduced libido, diminished clitoral sensation, and orgasmic dysfunction in women, can often accompany chronic inflammatory conditions, such as obesity, MetS, diabetes, and dyslipidemia. Hence, we recommend considering this in the comprehensive management of these conditions (***strong***). The use of phosphodiesterase type 5 inhibitors (PDE5i) in men with complaints of ED is recommended (***strong***), while the evidence is weak for the symptoms of hypolubrication in women (***weak***). Changes in lifestyles, such as quitting smoking (***strong***), reducing alcohol (***weak***), losing weight (***strong***), and increasing physical activity (***strong***) are generally recommended (***strong***) to improve sexual function.
**Recommendation #15:** We recommend changes in diet, especially adhering to the Mediterranean diet, which is rich in fruits, vegetables, nuts, whole grain, and olive oil, as opposed to processed grain and saturated fats common to the Western diet, which can improve sexual function in men and women with CVD or metabolic dysfunction (***weak***). We cautiously recommend bariatric surgery, which may improve some FSFI parameters in women with severe obesity (***weak***). We recommend psychological counseling to assess and manage body image issues, which may also improve sexual function (***weak***).

(*Continued*)

**Table 1.** Continued

**Recommendation #16:** Since hyperuricemia can be a marker of systemic metabolic disorder, we suggest including uric acid assessment in the diagnostic work-up of ED (***weak***), particularly in patients with obesity, MetS, or diabetes (***weak***). We recommend treating hyperuricemia and gout, if present, in patients complaining of sexual dysfunction, especially ED (***strong***). While there is reason to suspect that hyperuricemia-derived endothelial impairment can affect also vaginal lubrication (***weak***), further studies are necessary to solidify the association between gout and female sexual dysfunction.
**Recommendation #17:** Dissatisfaction with sexual activity is significantly associated with peripheral vascular disease. Therefore, using PDE5i to improve blood flow is suggested, as ***strong*** and ***weak*** recommendations in men and women, respectively. It is unclear how treatment of CVD or improvement in CVD symptoms may influence sexual function. We do not recommend antihypertensive drugs to treat sexual dysfunction (***weak***), as some of them (eg, beta-blockers, thiazides) are known to cause or exacerbate sexual dysfunction. However, hypertension must be adequately controlled, so the influence of antihypertensive drugs must be considered when evaluating sexual dysfunction (***strong***).
**Recommendation #18:** We recommend paying attention to the sexual consequences of chronic obstructive pulmonary disease (COPD)–related inflammation, low oxygen, and lower testosterone levels, as they may exacerbate ED (***strong***) and quality of sexual health (***strong***).
**Recommendation #19:** Given the frequent sexual side effects of antidepressant treatment, we suggest considering pharmacotherapy strategies (eg, switching to an antidepressant with less sexual-related side effects, dose reduction, augmentation, and adjunctive treatments like buspirone, when clinically possible) (***weak***). PDE5i may provide improvements in sexual dysfunctions in men with major depressive disorder with or without antidepressant treatment (***strong***).
**Recommendation #20:** We recommend the use of moisturizing and lubricating agents to combat Sjogren's syndrome (SS) symptoms, such as sexual lubricants (***weak***). Women with pelvic floor dysfunction should also consult a pelvic floor physical therapist (***strong***). We also recommend behavioral therapy in mitigating sexual distress (***weak***).
**Recommendation #21:** We recommend prompt diagnosis and proper treatment to minimize sexual dysfunction connected to autoimmune disease (***strong***). We also recommend supportive therapies for managing chronic autoimmune disease–associated sexual dysfunctions (***strong***).
**Recommendation #22:** We recommend that managing pain is critical to improving sexual function (***strong***), but agents used to treat chronic pain, such as opioids, gabapentinoids, selective serotonin reuptake inhibitors (SSRIs), and SNRIs, impair sexual function (***weak***). This must be considered in any workup for sexual dysfunction. For endometriosis, we suggest surgical removal of lesions when conservative therapies fail (eg. steroids), which can alleviate pelvic pain, at least temporarily (***weak***). Modulation of the endocannabinoid system (eg, treatment with CBD) may reduce inflammation in the context of endometriosis (***weak***), but more evidence is needed. Therefore, we do not recommend the use of CBD or similar products for endometriosis or other pain. We also recommend supportive therapies for managing chronic pain, which include psychological therapy, physical therapy, acupuncture, meditation, mindfulness, and cognitive behavior therapy (***weak***).
**Recommendation #23:** We recommend that vulnerable, eligible adults are promptly vaccinated for herpes zoster to prevent viral reactivation and risk of postherpetic neuralgia (PHN) (***strong***). Also, considering in light of the sexual dysfunction that may develop in patients with PHN, we recommend conservative treatment, followed by any of the above treatments for which there is strong evidence, only if conservative treatment fails.
**Recommendation #24:** We recommend reducing exposure to allergy-inducing agents (***weak***). We also recommend using vaginal dilators to recover function after vaginal injury due to radiation (***strong***), as well as strategies to reduce injury to vaginal and pelvic tissue, such as targeting and positioning strategies or performing radiation with a dilator in place to prevent unnecessary radiation exposure to sexual organs and tissue (***weak***).
**Recommendation #25:** The connection between CP/CPPS and sexual dysfunction has frequently been disregarded or not given sufficient attention, although well established (***strong***). Thus, we recommend that therapeutic strategies focused on symptom reduction, especially pelvic pain, should also be relevant to changes in sexuality (***strong***). Patients with CP/CPPS should be screened for overall reduced sexual function (***strong***), ED (***strong***), and premature ejaculation (PE) (***strong***). On the other hand, multiple partnerships and increased sexual frequency may facilitate the onset of this condition (***strong***).
**Recommendation #26:** We suggest caution when prescribing alpha-blockers, often the first therapeutic choice for CP/CPPS, as they may worsen sexual function due to ejaculatory dysfunction (***strong***). We also warn against several pain medications (opioids, SSRI) as they can also cause a decrease in libido (***strong***). There is no evidence regarding other treatment modalities, including phytotherapeutic agents such as pollen extract, quercetin, or saw palmetto. We suggest that pelvic floor rehabilitation may improve muscle resting tone and function, as well as reduce pain in CP/CPPS (***weak***).
**Recommendation #27:** We recommend that patients should be screened for psychosocial symptoms (eg, anxiety or stress) using either the psychosocial yellow flag system and/or Patient Health Questionnaire-9 (PHQ-9) and/or Generalized Anxiety Disorder-7 (GAD-7) scales (***strong***). If a clinically relevant level of psychosocial symptoms is observed, we recommend that a referral to a psychosocial specialist (eg, psychiatrist, specialist psychologist, or cognitive behavioral therapist) should be considered (***strong***). We recommend that psychological interventions focusing on pain reduction or adjustment to pain are to be implemented, potentially improving mood and function and reducing healthcare use (***weak***).
**Recommendation #28:** We suggest diagnosing and managing sexual symptoms in all chronic inflammatory diseases (***strong***).
**Recommendation #29:** We *suggest* that the presence of a couple, particularly if leveraging sexual health, can improve clinical management and outcomes when managing NCDs (***strong***). We *recommend* that both partners should maintain an open communication about the impact of NCDs, and related symptoms, on their sexual relationship (***strong***). We *suggest* the couple explore alternative forms of intimacy and sexual expression that are comfortable and satisfying for both partners, including trying new techniques, positions, or activities that minimize pain and discomfort or accommodate physical limitations in chronic inflammatory diseases. The partner can be actively involved in preventive measures, such as quitting smoking, eating a healthier diet, engaging in physical activity, and abstaining from alcohol, as well as supporting and encouraging adherence to the treatment plan (***strong***).

Abbreviations: CBD, cannabidiol; CP/CPPS, chronic prostatitis/chronic pelvic pain syndrome; CVD, cardiovascular disease; DAA, direct antiviral agent; ED, erectile dysfunction; HIV, Human Immunodeficiency Virus; MetS, metabolic syndrome; PDE5i, phosphodiesterase type 5 inhibitors; PID, pelvic inflammatory disease.

**Table 2.** The relative risk of sexually transmitted disease acquisition according to agent and oral/vaginal/anal sex.

| Infection/Etiological agent | Oral sex transmission risk | Vaginal sex transmission risk | Anal sex transmission risk |
|---|---|---|---|
| Chlamydia (*Chlamydia trachomatis*) | Low | High | Very high |
| Gonorrhea (*Neisseria gonorrhoeae*) | Moderate | High | Very high |
| Hepatitis B (HBV) | Low | High | Very high |
| Herpes simplex (HSV-1, HSV-2) | Moderate | High | Very high |
| Human immunodeficiency virus (HIV) | Low | High | Very high |
| Human papillomavirus (HPV) | Moderate | High | Very high |
| Syphilis (*Treponema pallidum*) | Moderate | High | Very high |
| Trichomoniasis (*Trichomonas vaginalis*) | Low | High | High |
| Mpox (Monkeypox) | Very high | High | Very high |

**Table 3.** Recommended treatments for the most common sexually transmitted infections (STIs).

| | |
|---|---|
| ***Chlamydia trachomatis*** | Doxycycline, 100 mg orally, BID for 7 days; or azithromycin, 1 g orally, in a single dose; or amoxicillin, 500 mg orally, TID for 7 days; or erythromycin, 500 mg orally, QID for 7 days; or ofloxacin, 300 mg orally, BID for 7 days; or tetracycline, 500 mg orally, QID for 7 days (***weak***). |
| ***Neisseria gonorrhoeae*** | Ceftriaxone 250 mg IM in a single dose plus azithromycin 1 g orally in a single dose: or cefixime 400 mg orally in a single dose plus azithromycin 1 g orally in a single dose (***weak***). It is recommended to treat *Trichomonas vaginalis* in men with metronidazole 2 g orally in a single dose. Alternative regimen for women and men: tinidazole 2 g orally in a single dose. No published randomized trials are available that compare these doses among men (***weak***). |
| ***Donovanosis*** | All treatment regimens should last for at least 3 weeks until full resolution of the lesions: azithromycin 1 gm orally once weekly or 500 mg daily; or doxycycline 100 mg orally BID; or erythromycin 500 mg orally QID; or trimethoprim-sulfamethoxazole 1 double-strength (160 mg/800 mg) tablet orally BID ***(weak)***. |
| ***Syphilis*** | Benzathine penicillin 2.4 million units IM (each buttock 1.2 million units—although some specialists recommend 2.4 U as a single injection) on day 1; or procaine penicillin 600 000 U IM daily for 10-14 days. In case there is an allergy to penicillin or aversion to parenteral treatment, doxycycline 200 mg daily (either 100 mg BID or as a single 200 mg dose) oral for 14 days; or tetracycline 500 mg orally QID for 14 days; or erythromycin 500 mg QID for 14 days. For LGV, treatment includes antibiotics such as doxycycline 100 mg BID for 21 days ***(weak)***. Alternative therapies include erythromycin, 500 mg orally, QID for 21 days; or azithromycin, 1 g orally, once weekly for 3 weeks with recommended test of cure 4 weeks after the completion of the treatment ***(weak)***. |
| ***Herpes*** | Acyclovir 400 mg orally TID for 7-10 days; or acyclovir 200 mg orally 5 times a day for 7-10 days; or famciclovir 250 mg orally TID for 7-10 days (***weak***). |
| ***Chancroid*** | Cefriaxone 250 mg IM in a single dose; or azithromycin 1 g orally in a single dose; or ciprofloxacin 500 mg orally BID for 3 days (contraindicated during pregnancy); or erythromycin 500 mg orally TID for 7 days. |
| **Monkeypox (Mpox)** | Even though several agents have been used for Mpox, currently, there are no approved treatments. While first-line treatment is supportive care with pain control and wound care, vaccination with the 2-dose MVA-BN vaccine series for persons aged 18 years and older at risk for Mpox has been recommended (***strong***). |
| ***HIV*** | Antiretroviral treatment (ART) regimens according to the Clinical Protocol and Therapy Guidelines of the Brazilian Ministry of Health[10] and from the Office of AIDS Research of the National Institutes of Health[11] for the management of HIV infection include 2 different substances: lamivudine and dolutegravir sodium (DTG) (***strong***). According to the WHO, the first-line ART preferred regimen includes DTG in combination with a nucleoside reverse transcriptase T-Inhibitor, recommended as the preferred first-line regimen for people living with HIV initiating ART, both in adults and adolescents (***strong***) and infants and children with approved DTG dosing (***weak***).[12] |

Abbreviations: BID, *bis in die* (twice a day); HIV, Human Immunodeficiency Virus; IM, intramuscular; LGV, lymphogranuloma venereum; QID, *quater in die* (4 times a day); TID, *ter in die* (3 times a day).

second–third most common sexually transmitted infection after chlamydia and trichomonas based on the Centers for Disease Control surveillance.[15] Transmission occurs through genital–genital, genital–anorectal, oro-genital, or oro-anal contact or by mother-to-child transmission at birth. The highest incidence of gonorrhea is in young adults (15-29 years), and there is a disproportionate burden of disease in ethnic minority groups and men who have sex with men.[16] Patient complaints are of urethritis, characterized by urethral inflammation, discharge of mucopurulent or purulent material, dysuria, and urethral pruritus. As with chlamydia, PID is a common complication of gonorrhea.

Trichomoniasis is a common STI caused by the protozoan *Trichomonas vaginalis*. In 2020, there were approximately 156 million new cases of *T. vaginalis* infection among people aged 15-49 years old (73.7 million in women, 82.6 million in men). Approximately one-third of new infections in this age group occur in the WHO African Region, followed by the Region of the Americas.[8] The majority of persons who have trichomoniasis (70%-85%) either have minimal or no genital symptoms, and untreated infections might last from months to years.[17] Men with trichomoniasis sometimes have symptoms of urethritis, epididymitis, or prostatitis, while women with trichomoniasis sometimes have vaginal discharge, which can

be diffuse, malodorous, or yellow green with or without vulvar irritation, and might have a strawberry-appearing cervix, which is observed more often on colposcopy than on physical examination.[18]

### *Genital ulcers*

Some sexually transmitted infections can result in characteristic genital ulcers, which can be either painful or painless. Estimates of the incidence of genital ulcers in the United States in 2018 report a median of 112 000 for syphilis and 6 354 000 for herpes.[15]

#### *Painless ulcers*

Infections causing non-painful lesions include the following:

- Donovanosis (granuloma inguinale), a bacterial infection caused by *Klebsiella granulomatis,* characterized by ulcerative lesions on the genital and perineal areas, which usually begin as painless nodules or papules that later break down into beefy-red ulcers with rolled edges and a firm, granulomatous base.[19] If left untreated, the infection can cause extensive tissue destruction, leading to scarring and permanent disfigurement of the genitalia.
  - Syphilis, caused by the bacterium *Treponema pallidum,* known for its painless chancres, which are lesions at the initial point of entry of the infection. Infection can be transmitted during vaginal, anal, and oral sex (Table 1). Short-term effects of syphilis on sexual life include a lack of sexual desire and loss of confidence in current and/or future sexual partners.[20] Chronic syphilis has been shown to cause obliterative endarteritis and interstitial inflammation in male genitalia. Although the effects on clitoral and vaginal blood supply have not yet been investigated, women may be affected similarly.
- Lymphogranuloma venereum (LGV) is a sexually transmitted infection caused by certain strains of *C. trachomatis* (serovars L1, L2, and L3). It primarily affects the lymphatic system and starts as a painless genital or rectal lesion that can progress to painful swelling of the inguinal lymph nodes, known as buboes.[21] The ulcers can become secondarily infected, causing discomfort and scarring. If left untreated, significant lymphatic obstruction can distort genital anatomy, resulting in conditions, such as a saxophone penis, where the penis becomes enlarged and distorted, resembling the shape of a saxophone.[22] Similarly, the vulva can become enlarged and thickened, sometimes leading to elephantiasis of the vulva.[23] Longstanding LGV can also cause strictures and fistulas months or years later. The presence of ulcers can cause pain during sexual activity, and the altered shape of the genitalia can lead to difficulties in achieving erections and participating in intercourse.
- Human papillomavirus and candidiasis will be discussed later.

#### *Painful ulcers*

- Genital herpes is caused by Herpes Simplex Virus (HSV) types 1 and 2 and is characterized by painful blisters or sores on the genital area. After the initial outbreak, the virus remains dormant and periodically reactivates due to different triggers, causing subsequent outbreaks. Typical areas affected by HSV include the labia majora, labia minora, perianal area, vaginal walls, and cervix. The area of a typical HSV outbreak is often painful, even before lesions appear, and can remain sensitive after the lesions disappear, causing dysuria and persistent pain.[24] Epstein–Barr virus can present as painful punched-out lesions on the vulva, often mistaken for HSV. Unlike HSV, EBV ulcers are not sexually transmitted; hence, the risk of misdiagnosis is high.[25]
- Chancroid is a highly transmittable disease but rare in developed countries.[26] Chancroid can be sexually transmitted or transmitted by skin-to-skin contact, potentially affecting other areas of the body. It is caused by the bacterium *Haemophilus ducreyi* and is characterized by soft, painful ulcers with ragged edges. In addition to painful ulcers, swollen lymph nodes (buboes) in the inguinal area are common, and these buboes can become infected and start draining. Pain associated with ulcers and buboes can cause discomfort during sexual activity. Healing ulcers may leave scars, which can lead to physical disfigurement and discomfort during intercourse, affecting body image and self-esteem.
- Mpox (formerly known as monkeypox), caused by *Monkeypox virus* (MPXV), is a zoonotic infection whose outbreak in 2022-2023 caused by the clade II MPXV has been declared a public emergency by the WHO. It primarily spreads through close skin contact and during the worldwide clade II outbreak, transmission most commonly occurred through sexual contact among gay, bisexual, and other men who have sex with men. Thirty-eight percent of cases have occurred in patients with HIV. Before the onset of the painful rash, prodromal symptoms include fever, lymphadenopathy, and myalgias. It can take up to 4 weeks for the wounds to re-epithelialize, making the patient infectious until full recovery. The disease may greatly impair physical comfort and psychological well-being, affecting sexual function.[27]

All patients who have genital ulcers should be evaluated in addition to a serologic test for syphilis and a diagnostic evaluation for genital herpes. In settings where chancroid is prevalent, a test for *H. ducreyi* should also be performed.[28] Specific tests for evaluation of genital ulcers include (1) syphilis serology (FTA-ABS and TP-PA) and either darkfield examination or direct immunofluorescence test for *T. pallidum*, (2) culture or antigen tests for HSV, and (3) culture for *H. ducreyi*. Genital herpes, syphilis, and chancroid have been associated with an increased risk of HIV transmission. The combination of painful genital ulcers (1 or more) and tender suppurative inguinal adenopathy suggests the diagnosis of chancroid.

### *Hepatitis B virus*

The WHO estimates that 296 million people were living with chronic HBV infection in 2019, with 1.5 million new infections each year. In 2019, HBV resulted in an estimated 820 000 deaths, mostly from cirrhosis and hepatocellular carcinoma (primary liver cancer).[8] Hepatitis B virus is a highly infectious agent, transmitted through percutaneous (puncture through the skin) or mucosal (direct contact with mucous membranes) exposure to infectious blood or body fluids during sex with an infected partner, unsafe injections, or exposures to sharp instruments. Most people do not experience any symptoms when newly infected. Some people have acute illness with symptoms that last several weeks including yellowing of the skin and eyes (jaundice), dark urine, feeling very tired, nausea, vomiting, and pain in the abdomen. It is not possible on clinical grounds to differentiate hepatitis B from hepatitis

caused by other viral agents. Hence, laboratory confirmation of the diagnosis is essential. Persons with chronic infection (eg, those with persistent hepatitis B surface antigen (HBsAg) in the serum for at least 6 months following acute infection) serve as the main reservoir for HBV transmission.[29]

### *Hepatitis C virus*

Hepatitis C virus (HCV) has a relevant global impact in terms of morbidity, mortality, and economic costs, with more than 71 million people infected worldwide.[30] Hepatitis C virus is primarily transmitted through blood-to-blood contact, but it can also be spread through sexual contact mainly in individuals with multiple partners or those who practice unprotected sex. The risk of HCV may increase with the presence of other STIs in people who inject drugs, sex workers, transgender individuals, and men who have sex with men.[31] After identifying HCV and studying its features, interferon-alfa and ribavirin became primary treatment options for all patients with chronic HCV infection. However, due to their limited coverage against different HCV genotypes, ethnic variations, and suboptimal sustained virological response, the development of direct-acting antiviral agent (DAA) therapy became essential.[32]

### *Human immunodeficiency virus*

Human immunodeficiency virus is a retrovirus infecting CD4+ lymphocytes, which are pivotal to cell-mediated immunity. Those most affected in North America, Western Europe, and Australia are men who have sex with men and intravenous drug users. In the developing world, heterosexual intercourse and vertical transmission (mother to child) remain the primary routes of transmission.[33] Sexual difficulties are common in patients with HIV, including erectile dysfunction (ED), loss of libido, and ejaculatory disorders.[34] Having a healthy sex life after an HIV diagnosis can be difficult, as stigma for transmission may act as a barrier to sexual activity, particularly in at-risk populations, such as men having sex with men.

Vulnerabilities to HIV/STIs include unprotected sexual intercourse, lack of disclosure, failure to undergo counseling and testing, and multiple concurrent sexual partners. Men and women with HIV who have multiple sexual problems are likely to suffer from major depression.[35] There are many other factors at play, including social stigma, mental health disorders, substance use, lipodystrophy, arteriosclerosis, changes in sex hormone levels, and peripheral neuropathy, which tend to occur at a higher frequency in HIV+ individuals.[36,37]

The use of harm reduction strategies[38] for patients with HIV infection, particularly those involving substance use, may play a critical role in overall health management and infection prevention. These strategies include comprehensive approaches to reduce drug abuse and excessive alcohol consumption, which are significant risk factors in the HIV-positive population. The use of pre-exposure prophylaxis, such as daily oral tenofovir/emtricitabine, has been strongly recommended for high-risk individuals, significantly reducing HIV transmission rates when adherence is high.

### *Human papillomavirus*

Human papillomavirus is sexually transmittable and, depending on the strain, can lead to the formation of warts or cause cervical cancer. An estimated 604 000 cases of cervical cancer were diagnosed among women worldwide in 2020, most of which are linked to infection with high-risk human papillomavirus (HPV).[39] Human papillomavirus can also cause anogenital or penile warts and certain types of cancer among men.[40] There are more than 200 known genotypes of HPV, which are responsible for both benign and malignant tumors; approximately 40 types infect the anogenital tract and are among those considered at high oncogenic risk, with HPV6 being the most frequent genotype (70%).[41] Being diagnosed with HPV carries the risk of worsening sexual function, due to genital appearance, decrease in sexual desire and frequency of intercourse, fear of cancer, and the possible need for surgical interventions.[42]

### *Other infections*

*Ureaplasma urealyticum* and *Mycoplasma genitalium* are both sexually transmitted and can affect the vagina and urethra, causing abnormal discharge and pain. As with other chronic prostatic infections, they have also been found in the prostatic fluid of patients with premature ejaculation (PE).[43] In the long term, they may contribute to infertility[44] and recurrent miscarriages. Candidiasis is not considered sexually transmittable but can cause sexual dysfunction in both men and women due to the variety of uncomfortable symptoms, including uncomfortable vaginal discharge and balanoposthitis.[45] Recurrent vulvovaginal candidiasis can significantly affect sexual satisfaction and orgasm.[46] Similarly, bacterial vaginosis, caused by overgrowth of Gardnerella due to pH imbalance, is associated with a fishy odor, can cause vaginal discomfort, decreased sexual function, and impaired self-esteem,[47] with the duration of the disease having the greatest impact on sexual dysfunction, and the treatment of the disease bearing significant beneficial impact on the sexual function itself.[48]

The diagnosis of an STI in the context of a couple's relationship can trigger disagreements due to sexual intercourse involving other people, with possible consequences for the couple's relationship. Extra couple sexual activities need to be consensual and mutually agreed upon in open relationships (polyamorous). Usually, feelings of guilt and betrayal follow these diagnoses, and healthcare providers need to address these situations empathetically.[49]

### *COVID-19*

SARS-CoV-2, or severe acute respiratory syndrome coronavirus 2, is part of the Coronavirus family and is responsible for COVID-19, a highly contagious respiratory illness that led to a global pandemic. While COVID-19 primarily affects the respiratory system, it can affect sexual health through various mechanisms, both direct and indirect.[50] Transmission of SARS-CoV-2 occurs predominantly through close contact with aerosols and respiratory droplets of an infected individual. SARS-CoV-2 RNA has also been detected in several body fluids, including saliva (83%), feces/rectal swabs (32%), urine (3.8%), vaginal secretions (2.7%), and semen (1.6%).[51]

Endothelial dysfunction is among the main determinants of SARS-CoV-2; the endothelium expresses the protein angiotensin-converting enzyme 2 (ACE2), which facilitates viral entry.[52] Vascular integrity is necessary for sexual and, particularly, for erectile function. Hence, resulting vascular damage may be among the leading causes of an increased risk of experiencing ED among COVID-19-affected men.[53] Results from pooled analysis have shown that in COVID-19 patients, the relative risk of developing ED is 2.64 times greater than in patients without COVID-19.[54] In addition

to ED, direct testicular injury, hypogonadism, anosmia and ageusia, impaired pulmonary hemodynamics, generalized inflammatory status, and psychological burden are considered to be implicated in the etiopathogenesis of COVID-19.

Direct testicular damage can occur after COVID-19 infection, with possible orchitis-like syndrome and spermatogenesis damage. There is evidence, although limited, that a significant increase in serum luteinizing hormone (LH) levels and a dramatic decrease in the serum testosterone (T) to LH ratio occurs in COVID-19 patients compared to age-matched healthy men.[55] Both ACE2 and the transmembrane protease, serine 2 (TMPRSS2) are crucial for viral entry and are highly expressed in the male genital tract (seminiferous ducts cells, spermatogonia, Leydig and Sertoli cells, and prostate epithelial cells), while both are modulated by T activity.[56] Sperm quality was found to be significantly impaired in men with COVID-19 compared to controls, but long-term data about the effects on seminal parameters are inconclusive.[57]

The pandemic also led to changes in sexual behavior among individuals and couples.[58] With lockdowns, social distancing measures in place, and fears of virus transmission, many people experienced reduced opportunities for in-person sexual encounters. On the one hand, it has been suggested that a decrease in sexual frequency and casual sexual encounters due to restrictions on social gatherings may have had unexpected sexual health benefits, in part due to reductions in STI rates.[59] Conversely, other studies have reported an increase in sexual desire, intimacy, and experimentation within established partnerships, as couples spent more time together during lockdowns.[60] This dichotomy highlights the complexity of how the pandemic has influenced sexual behavior and relationships. Research has documented increased levels of anxiety, depression, and stress[61] during the pandemic, which have been shown to negatively affect sexual desire and satisfaction.[62] However, some individuals and couples reported using intimacy as a coping mechanism, emphasizing the importance of addressing mental health alongside sexual health concerns during crises.[63]

Vulnerable populations, such as marginalized communities, individuals with limited access to healthcare and ethnic, sexual, and gender minority groups, faced heightened risks during the pandemic.[64] For example, the LGBTQ+ community experienced disruptions in access to gender-affirming care and sexual health services, exacerbating existing health disparities.[65] Moreover, they also reported a significantly higher proportion of depression, anxiety, and COVID-19-associated physical symptoms, in line with pre-pandemic data that highlight the vulnerabilities of sexual and gender minorities.[66]

Finally, a non-negligible percentage of individuals experience long-lasting symptoms even after recovering from the acute phase of COVID-19, a condition commonly referred to as "long COVID." Symptoms of long COVID can be diverse and may include persistent fatigue, brain fog, and muscle pain, all of which can affect sexual health, defined as sexual long COVID (SLC) syndrome.[67] Women with long COVID reported significantly worse arousal, lubrication, orgasm, and pain with respect to women with COVID-19 who did not develop long COVID.[68]

## Male and female inflammation and sexual function

Inflammation is part of a protective response to injury or infection, triggering "sickness behaviors," which help to facilitate survival through energy preservation and other protective responses during illness.[69,70] However, when triggered persistently, inflammation is detrimental to general health and, particularly, to sexual function. A plethora of studies have established a link between chronic inflammatory conditions, such as metabolic syndrome, obesity, diabetes, hypertension, and male and female sexual dysfunction.[71,72] A central feature of these conditions is low-grade chronic inflammation, a persistent inflammatory response that can cause endothelial cell damage and subsequent vascular dysfunction.[73] The identification and measurement of inflammatory biomarkers are imperative for gauging the decline in vascular health. Quitting smoking and dramatically reducing alcohol intake, coupled with an active lifestyle and healthy dietary habits, particularly the consumption of anti-inflammatory foods, have emerged as potential mitigators of chronic inflammation.

Each part of this section will be devoted to an inflammatory condition or a group of interrelated inflammatory disorders, providing a brief introduction to the epidemiology and clinical presentation and then discussing specific recommendations.

### *Obesity, metabolic syndrome, diabetes, and dyslipidemia*

There is a high strength of evidence that prolonged inflammation, which occurs commonly in obesity, metabolic syndrome (MetS), diabetes, and dyslipidemia, leads to vascular damage that reduces blood flow to the genitalia.[74,75] In fact, these conditions foster a pro-inflammatory state that precipitates damage to endothelial cells lining the vasculature. The production of inflammatory mediators such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-$\alpha$), and C-reactive protein (CRP) is often elevated in individuals with metabolic disease. When healthy, the endothelium regulates vascular tone and blood flow through nitric oxide (NO), which is the main mediator of cavernosal relaxation. Nitric oxide activates neuronal and endothelial NO synthase, which, in turn, activates soluble guanylyl cyclase. This increases the concentration of cyclic guanosine monophosphate, resulting in the activation of protein kinase G. However, persistent inflammation disrupts these functions, leading to impaired vasodilation and a cascade of vascular impairments.[76-78] The relationship between diet and endothelial health is both complex and critical. Diets rich in anti-inflammatory foods such as fruits, vegetables, and omega-3 fatty acids can protect against chronic endothelial inflammation. Conversely, diets high in processed foods and saturated fats can exacerbate the inflammatory state and accelerate endothelial damage.[79]

Excess body adipose tissue, especially visceral adipose tissue, poses a significant threat to individual health. In particular, visceral lipid accumulation as measured by the "visceral adiposity index"[80] and by the "lipid accumulation product"[81] is a combination of lipid parameters and anthropometric measurements that predict an inflammatory-based and adiposity-related cardiometabolic risk and, at the same time, the risk of sexual dysfunction.

For these reasons, men and women with obesity, MetS, diabetes, and dyslipidemia consistently present with lower scores on several sexual psychometric tools, such as the International Index of Erectile Function (IIEF-15) and the Female Sexual Function Index (FSFI).[82,83] As body mass index (BMI), waist size, diastolic blood pressure, triglycerides, and glycated hemoglobin (HbA1c) decrease and high-density lipid (HDL)-cholesterol levels increase, sexual quality

improves.[77,84] The beneficial effects go beyond weight loss and metabolic improvements, as they may also be linked to increases in sex hormones, namely, dihydroepiandrosterone (DHEA) and T, levels of which tend to wane in obese individuals.[85] Finally, the role of body image cannot be ignored, as low self-esteem and a negative body image often accompany metabolic diseases connected to obesity and high BMI, particularly in women, which also impact sexual function.[86]

### *Gout*

Hyperuricemia is a medical condition characterized by abnormally high plasma levels of uric acid, a breakdown product of purines. Several factors can contribute to the development of hyperuricemia, including a diet high in purine-rich foods, such as red meat, organ meats, seafood, and certain alcoholic beverages (especially beer), genetic predisposition, certain medications (eg, beta-blockers, diuretics), and concomitant diseases, such as chronic kidney failure, diabetes, and MetS.[87,88] When a chronic elevation of uric acid levels persists above the saturation point for monosodium urate crystal formation, deposition of crystals occurs, resulting in gout. Crystals can accumulate in joints and other tissues, causing painful arthritis and eventually, if left untreated, can lead to the development of kidney stones and kidney damage. The reported prevalence of gout worldwide ranges from 0.1% to approximately 10%, being relatively common (1%-4%) in North America and Europe, and almost 2-fold more prevalent in men than women.[89]

Recent research has suggested a potential link between hyperuricemia and sexual dysfunction, particularly ED, which is present in 33% of men with hyperuricemia, according to meta-analyzed data.[90,91] While hyperuricemia represents a cardiovascular risk factor that negatively impacts sexual health, several other mechanisms have been implicated in the onset or worsening of sexual dysfunction,[92] including a chronic inflammatory state, endothelial function impairment, and psychological distress.

### *Cardiovascular disease*

Cardiovascular disease (CVD) negatively impacts male and female sexual function and can present by itself, while it is often comorbid with or stems from metabolic disorders.[74,93] A chronic inflammatory state induces oxidative stress and metabolic abnormalities that contribute to atherosclerotic plaque formation, hypertension, and, eventually, major adverse cardiovascular events (MACEs).[94,95] These plaques not only physically represent the effects of the inflammation and the decline in endothelial health, but they can also disrupt blood flow to the genitals, impeding erectile function, arousal, clitoral sensation, and orgasm.[96] Interestingly, for anatomical and physiological reasons, these sexual symptoms often precede the MACE, up to several years.[97]

Although there are fewer studies in women compared to men, there is direct evidence from patient biopsies of clitoral cavernosal tissues that demonstrate vascular abnormalities in the presence of CVD. Doppler histogram analysis of heavy smokers, who have a higher incidence of CVD, showed significantly reduced blood flow and hemodynamics indices in the clitoral body and labia minora.[98]

Cardiovascular disease results in inflammatory damage to the endothelium, a mechanism known as another equation

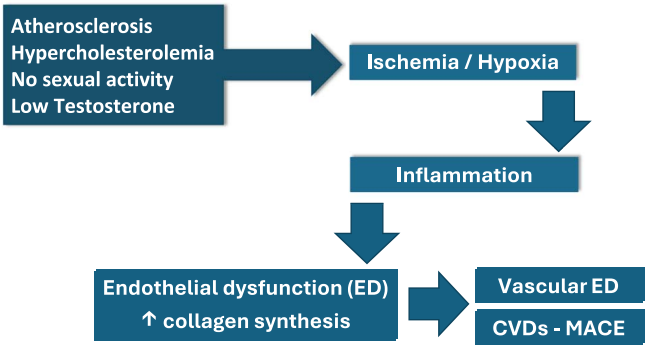


**Figure 2.** ED = ED. several systemic factors produce the ischemic peripheral reaction in the vessels, stimulating the inflammation of the endothelium (ED) and the neo-synthesis of collagen in the place of the endothelium itself. This produces erectile dysfunction (ED) and other cardiovascular diseases (CVDs) and, later, the major adverse cardiovascular events (MACE).[99]

ED = ED, where the endothelial dysfunction (ED) equals the erectile dysfunction (ED) (Figure 2).

### *Oncological diseases*

As oncosexology is a specific topic researched by another ICSM committee, we would like just to mention here that, again, inflammation is both a risk factor and a consequence of neoplasia and that this is one of the multifaceted reasons for the bidirectional association between cancer and sexual dysfunction.

### *Respiratory diseases*

Chronic inflammation is a key driver in the development and progression of respiratory diseases, such as chronic obstructive pulmonary disease (COPD) and asthma, due to a combination of genetic susceptibility and environmental influences, including exposure to pollutants, allergens, and infectious agents.[98] The inflammatory process in respiratory diseases also involves the activation of the nuclear factor-kappa B (NF-$\kappa$B) pathway, which plays a crucial role in regulating the expression of pro-inflammatory genes. This activation leads to the production of cytokines such as TNF-$\alpha$, IL-6, and IL-8, which contribute to the chronic inflammatory environment and the subsequent respiratory symptoms,[100] as well as endothelial impairment. Furthermore, chronic inflammation can cause systemic effects, including cardiovascular diseases, which are common comorbidities in patients with respiratory diseases.[101] This creates a common ground for the development of sexual dysfunction and conveys an increased risk of ED in men, due to the reduced availability of NO and increased oxidative stress, which impairs vascular function.[85] In women, inflammation can interfere with sexual desire and arousal by affecting hormonal balance, vascular health, and psychological wellbeing.[102] Additionally, the chronic fatigue, pain, and psychological stress associated with chronic inflammatory diseases can further diminish sexual desire and performance.

In summary, chronic inflammation in respiratory diseases involves complex mechanisms that lead to persistent immune activation and tissue damage. This inflammatory state worsens respiratory health and impacts sexual function by disrupting vascular, hormonal, and psychological processes.

### *Depression*

Mood disorders have been only recently added to the list of typical NCDs that lead to sexual dysfunction (eg, metabolic, CVD, oncological, and respiratory). Once again, inflammation appears as a major linking factor.[103]

First, depression risk is 2-4-fold higher in patients with NCDs with respect to the normal population.[104] Second, depression is associated with NCD risk factors (eg, alcohol consumption and tobacco smoking or dependence, poor diet, reduced physical exercise) and other underlying mechanisms (eg, inflammation and abnormalities of the stress response system). Depression also negatively affects the treatment of other NCDs.[105] Moreover, antidepressants, along with several psychiatric drugs, mainly for serotoninergic and/or antidopaminergic actions, may negatively impact sexual function during[106] and after[107] treatment. Finally, depression is a major risk factor for and consequence of them,[108] further representing the endless cycle by which lifestyle, inflammation, NCDs, and sexual dysfunctions influence one another.

### *Autoimmune disorders*

Autoimmune disorders are a common cause of sexual dysfunction. The innate immune system plays a pivotal role in vascular impairment and inflammation. Toll-like receptors (TLRs) recognize pathogen-associated molecular patterns, leading to the activation of inflammatory pathways that contribute to endothelial dysfunction and atherosclerosis. This systemic inflammatory response sets the stage for further vascular injury and sexual dysfunction.[72]

For instance, Sjogren's syndrome (SS) is a crippling disorder that causes inflammation and dysfunction in glands, such as the lacrimal and salivary glands. Sjogren's syndrome is the second most common autoimmune rheumatic disease and tends to occur in post-menopausal women. It significantly reduces both quality of life and sexual function.[109] Patients with SS suffer from chronic dry mouth and dry eye, pelvic floor dysfunction, vaginal or cervical atrophy, and often severe vaginal dryness. As the severity of vaginal dryness increases, FSFI scores decline, particularly in patients that tend to self-blame, ruminate, and catastrophize.

Similar to SS, women with systemic lupus erythematosus (SLE), another common autoimmune disorder, experience poorer sexual function with negative illness perceptions. Patients with rheumatoid arthritis also have impaired sexual function, largely attributed to the accompanying pain and fatigue, but depression, anxiety, and poor body image are also contributing factors. Moreover, rheumatoid arthritis, SLE, and multiple sclerosis, another autoimmune disorder, can lead to ED with ***weak,***[110] ***strong,***[111] and ***weak***[112] evidence, respectively.

Other conditions linked with sexual dysfunction, such as fibromyalgia, may appear as inflammatory diseases.[113] However, the role of autoimmunity is still undetermined, but it is deemed to influence sexual function also through more indirect ways. For example, patients with rheumatoid arthritis also have impaired sexual function, largely attributed to the accompanying pain and fatigue, while depression, anxiety, and poor body image are also contributing factors.[114]

### *Chronic pelvic pain*

Chronic pelvic pain is a common condition affecting at least 26% of women, resulting in significant sexual dysfunction, most patients suffering years before diagnosis, and some never receiving targeted treatment. Representative conditions, such as vulvodynia and endometriosis, historically have been considered separate entities based on their underlying causes, but more recent investigations suggest that they may share a common thread. They both involve neuro-inflammation that leads to chronic pain.[115] Vulvar inflammation is associated with chronic tissue changes, such as neuroproliferation within the vestibule, burning, vulvovaginal pain, and prohibitive superficial dyspareunia. The etiology of endometriosis is also incompletely understood, but it clearly negatively impacts sexual function.[116] The growth of uterine tissue outside the uterus can cause significant inflammation, while inflammation may help to encourage the growth of these tissues and trigger or exacerbate pain signaling.[117]

Although the etiology of interstitial cystitis/chronic bladder pain syndrome (IC/BPS) is incompletely understood, women with bladder pain often present with clinical and urinary biomarkers of neuroinflammation, which is associated with neuropathic pain and other sensory symptoms that impair sexual function.[118] Despite the orgasm-induced release of endogenous opioids,[119] patients living with chronic pain tend to experience reduced sexual function due to the condition itself, the consequent depression, or the drugs used to manage pain.[120,121]

However, non-steroidal anti-inflammatory drugs (NSAIDs) and steroid treatment are ineffective and, in the case of topical steroids, are not well tolerated by patients with vulvodynia.[122] Recent evidence shows that targeting inflammation may only address part of the underlying mechanism of disease, which also involves lipid dysregulation and transient receptor potential cation channel subfamily V (TRPV) signaling.[123] Currently, there are no medical therapies with level 1 evidence.[124] Vestibulectomy (surgical removal of the vestibule) is effective for patients with localized pain (***weak*** *evidence*), but it does not apply to all disease subtypes, is not performed in all countries, and is highly invasive, requiring significant recovery time and cost.

Beyond surgical resection of implants and hormonal pain management, several points of emerging evidence suggest that cannabis may have a role in the treatment of endometriosis pain due to its anti-inflammatory, anti-oxidative, and anti-angiogenic effects.

### *Postherpetic neuralgia*

Postherpetic neuralgia (PHN) is a common complication of herpes zoster (shingles) infection, which often occurs in older adults (≥50 years old) who were previously infected with varicella zoster (chickenpox).[125] PHN is characterized by debilitating pain lasting >90 days following reactivation of latent varicella zoster as herpes zoster, which manifests as a neurocutaneous dermatomal vesicular disease with radicular pain. Lesions can appear on any body site but most often occur on the trunk or buttocks. The data are limited, but there is some weak evidence that herpes zoster and PHN can negatively impact erectile function.[126]

Conservative medical therapies for PHN include oral NSAIDs, tricyclic antidepressants, pregabalin, gabapentin, serotonin–norepinephrine reuptake inhibitors (SNRIs), tramadol, topical lidocaine, or capsaicin. When these fail, various interventional treatments have been tried including subcutaneous botox (***strong*** *evidence*), transcutaneous electrical nerve stimulation (***strong*** *evidence*), intrathecal injection of

lidocaine or midazolam (***strong***), dexamethasone injection into 3-5 DRG segments (***strong*** *evidence*), pulse radiofrequency (***strong*** *evidence*), spinal cord stimulation (***weak*** *evidence*), peripheral nerve stimulation (***weak*** *evidence*), and paravertebral block (***weak*** *evidence*).[127] Vaccination is the most effective treatment to *prevent* PHN (***strong*** *evidence*), but it must be administered prior to developing PHN.

### *Vulvovaginal dermatoses and injury*

Vulvovaginal dermatoses (eg, lichen sclerosus),[128] allergies to agents introduced to the vagina (eg, semen),[37], and other inflammatory diseases that can disfigure the genitalia (eg, hidradenitis suppurativa)[129] also impede sexual function. Injury, such as that caused by pelvic radiation, can result in inflammation that impairs sexual function.[130]

### *Prostatitis*

Prostatitis is a common condition, with 35%-50% of men reported to be affected by symptoms during their lifetime.[131] Prostatitis has garnered increasing attention in the medical community due to its potential repercussions on various aspects of men's health. Prostatitis is classified as acute bacterial prostatitis (category I), chronic bacterial prostatitis (category II), chronic prostatitis (CP)/chronic pelvic pain syndrome (CPPS, category III), and asymptomatic inflammatory prostatitis (category IV) according to the National Institutes of Health prostatitis classification system.[131-133]

A universally recognized "gold standard" for definitively diagnosing CP/CPPS does not exist. Diagnosis is typically established through a comprehensive assessment of patient history, symptoms, and the exclusion of alternative causes. Patients can be categorized as being in the early stages of the disease if they have encountered persistent, recurring symptoms for less than 6 months and have not yet received antibiotic treatment or in the later stages of the disease if they have experienced persistent, recurring symptoms for more than 6 months and have not responded to initial pharmacotherapy. Chronic prostatitis is not contagious and is not classified among sexually transmitted diseases. However, multiple sexual partnerships are significantly associated with increased odds of a CP diagnosis.[134]

The UPOINT clinical phenotypic classification system has been devised to address the complexity of CP/CPPS, prioritizing a diverse range of symptoms. This system categorizes patients into 6 clinical domains: urinary, psychosocial, organ-specific, infection, neurologic/systemic, and muscle tenderness. Despite its success in significantly enhancing symptom management, the ongoing discussion revolves around the potential addition of a sexual dysfunction domain to the UPOINT system.[135] For instance, ejaculatory pain is recognized as a common feature of men with CP/CPPS, affecting 58% of patients with prostatitis, and, in some men, ejaculatory pain may be the only manifestation of prostatitis.[136] Moreover, several studies have found an increased association between CP/CPPS and ED or PE.[80,81,85]

The underlying mechanisms of CP/CPPS-associated sexual dysfunction remain unclear.[137] Vasculogenic, endocrine, and neurogenic factors, as well as psychological factors, may play an important role in the pathogenesis of sexual dysfunction in CP/CPPS (Figure 3). Individuals with CP/CPPS are more prone to experiencing vascular endothelial dysfunction compared to asymptomatic controls.[138] This contributes to the occurrence of sexual dysfunction within these populations. Psychological factors contribute significantly to sexual dysfunction in individuals with CP/CPPS, leading to increased levels of depression and impaired sexual function in affected men.[139] Another plausible explanation for the elevated prevalence of ED among men with chronic pelvic pain may be linked to the presence of abnormally high resting pelvic floor muscle tone (Figure 4). This condition is frequently observed in men with both sexual dysfunction and sexual pain disorders. It is believed that elevated pelvic floor muscle tone could hinder normal erectile function by potentially obstructing arterial inflow to the penis through extrinsic muscular compression. It is also known as pelvic floor overactivity, and it is encountered in up to 50% on physical examination of men with CP/CPPS.[140,141]

### *Other chronic inflammatory conditions*

Clearly, chronic inflammation plays a pivotal role in sexual dysfunction and in NCDs, as demonstrated by the associations between ED and specific inflammatory markers, including C-reactive protein,[142] or the neutrophil/lymphocyte and platelet/lymphocyte ratios.[143] These work as biomarkers of severity of both inflammation and sexual dysfunction, such as ED. Hence, virtually all other inflammatory diseases are candidates to produce sexual dysfunction. While, at first glance, it may appear that women suffer fewer sexual consequences from inflammation, this is unlikely. The major limitation to understanding the impact of inflammation on female sexual function is the lack of research in this area. None of the available evidence rises above moderate because there are no adequately powered clinical studies and no RCTs pertaining to the influence of inflammation on sexual dysfunction in women. This area of research is in its infancy. However, as presented herein, the available literature strongly suggests that the vascular damage caused by chronic inflammation has similar effects in women, reducing blood flow to the clitoris and possibly impairing orgasm and overall sexual pleasure.[74,93,144] Furthermore, the sexual response cycle in women is particularly susceptible to the indirect effects of inflammation, such as fatigue, pain—even pain that does not affect genitalia—depression, low energy, and reduced self-esteem or body image issues.[145]

Chronic kidney disease (CKD) can lead to ED through vascular dysfunction, resulting in an impaired endothelium and reduced NO production (***strong*** *evidence*).[146] Additional contributors to ED in CKD include oxidative stress, inflammation, hypogonadism, hyperprolactinemia, and buildup of uremic toxins.[147]

Crohn's disease and ulcerative colitis are inflammatory bowel diseases (IBDs) that can cause chronic inflammation and may have an impact on ED[148] (***weak*** *evidence*).

Chronic inflammation, including chronic periodontitis (severe gum disease), is associated with a higher risk of ED (***weak*** *evidence*).[149]

Penile modifications, such as the injection of materials like fat, silicone, polymethyl methacrylate, and hyaluronic acid into the penis, have been reported to cause infection and inflammatory reactions such as the formation of sclerotic lipogranuloma and thus run the risk of inducing sexual dysfunction (***strong*** *evidence*).[150]

### *The "anti-inflammatory role" of the couple*

Certainly, the management of chronic inflammation–derived sexual dysfunctions can benefit from a collaborative effort

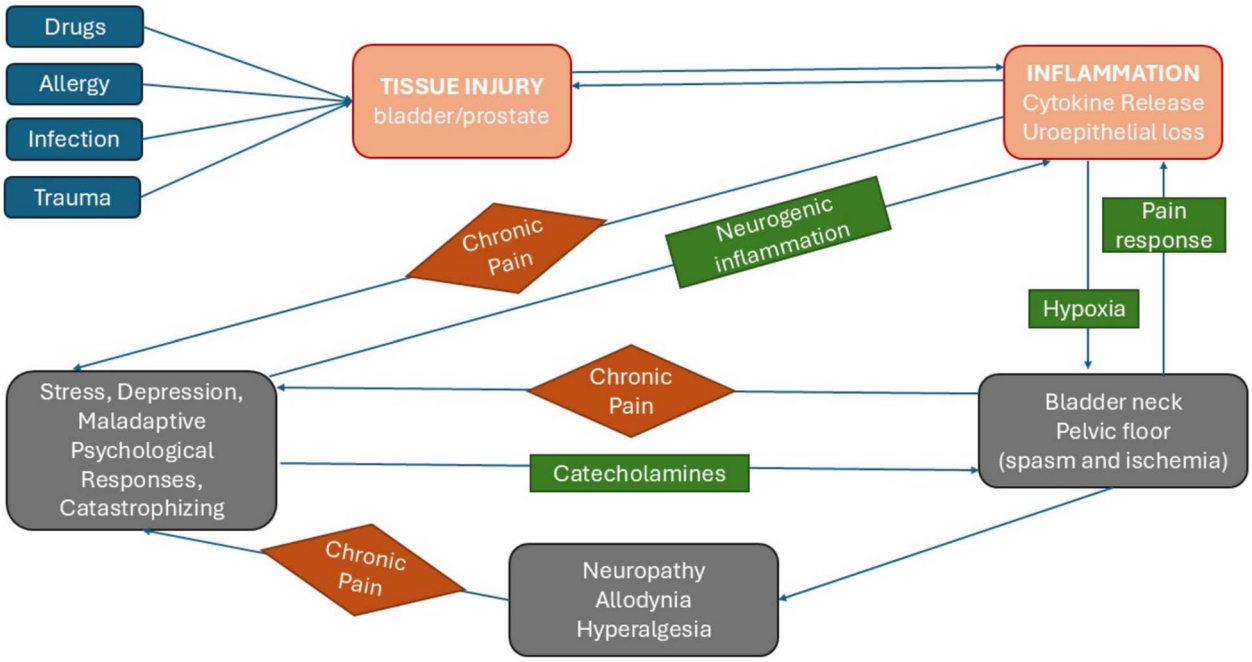


**Figure 3.** Multifactorial etiology of chronic pelvic pain syndrome. Adapted from.[136]

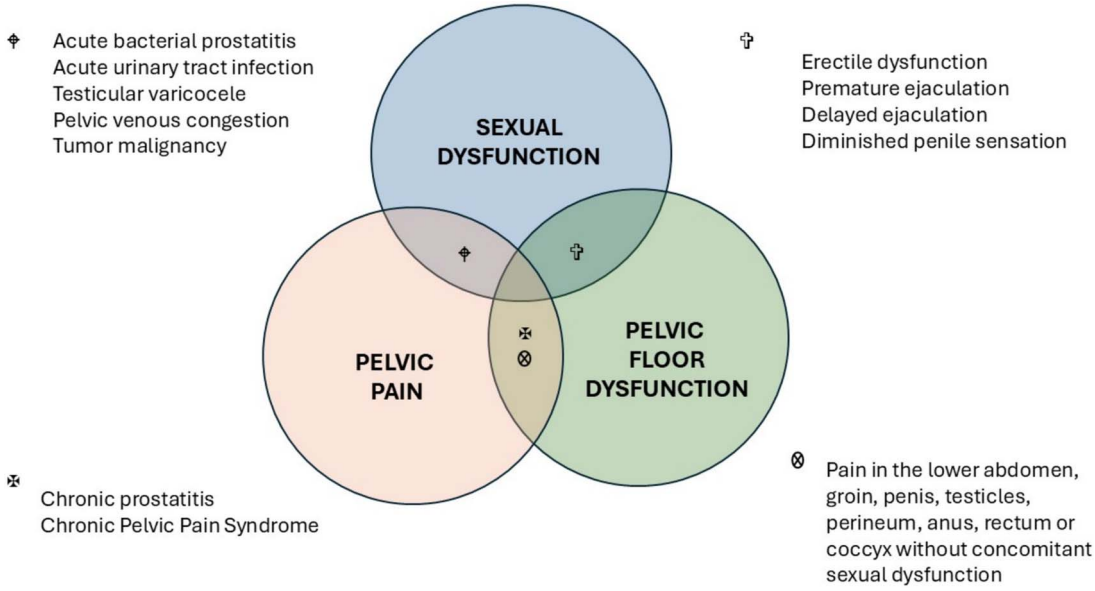


**Figure 4.** Associations between commonly observed elements of male sexual dysfunction, pelvic floor dysfunction, and pelvic pain. Adapted from.[140]

between the affected individual and their partner, which together as a couple can have a "pro-" or an "anti-inflammatory" role.[151] Indeed, evidence from studies on chronic illnesses highlighted that targeting both patient and partner may enhance the efficacy of pharmacological, lifestyle, and psychosocial interventions.[152,153] Indeed, the sexual health of a partner can dramatically impact the sexual function of their partner.[154] Meta-analyzed data report that men partnered with women with female sexual dysfunction (FSD) have an increased risk of erectile and ejaculatory dysfunction, while there is evidence that FSD may impair men's sexual desire and orgasmic function.[155] Discussing concerns, fears, and feelings can foster understanding and support, helping to relieve psychological distress and anxiety related to sexual difficulties.

### *Final remarks*

Clearly, inflammation plays both direct and indirect roles in impeding sexual function, although there is a paucity of well-designed RCTs, which is why there is almost no level 1 evidence. While acute inflammation may resolve naturally or can be resolved with anti-inflammatory agents, chronic inflammation is a vexing problem. Reducing inflammation by quitting smoking, increasing physical activity, implementing diet changes, fostering weight loss, and counseling patients

with mood disorders and poor body image or negative sexual feelings may also help to ease sexual dysfunction. In this fascinating field of sexual medicine, significantly more research needs to be conducted to fully understand how inflammation affects sexual function.

The WHO called for a global action plan for the prevention and control of NCDs, aiming for a 25% relative reduction in premature mortality by 2025 (the so-called "25 × 25 goal") through targeted action on 7 risk factors (tobacco use, excessive use of alcohol and drug abuse, physical inactivity, poor diet and excessive sodium intake, elevated blood pressure, obesity, and diabetes[156]). Unfortunately, the goal will not be reached next year for several reasons. We postulate here that the WHO's call, grounded in the principle that chronic inflammation can be reduced through lifestyle changes, lacked, as frequently happens, attention to sexual health. Since changes in lifestyle can fail due to a lack of motivation, the missed opportunity to use sexual health as motivation demonstrates that medicine, without sexual medicine, is not comprehensive medicine.[157]

## Conclusions

In conclusion, the Fifth ICSM Committee on Infection, Inflammation, and Sexual Function in Male and Female Patients has extensively reviewed and highlighted the complex interplay between infection, inflammation, and sexual dysfunction in both genders, in the LGBTQ+ community, and in couples. Our findings underscore the significant impact that various infectious and inflammatory conditions can have on sexual health, manifesting as a range of dysfunctions that can profoundly affect the quality of life and intimate relationships. This comprehensive evaluation stresses the importance of recognizing these conditions as potential contributors to sexual dysfunction and advocating for integrated approaches in diagnosis and treatment. Addressing these underlying health issues can dramatically improve sexual function and enhance overall wellbeing, emphasizing the necessity for healthcare providers to be aware of these connections in their clinical practices. The SM = SM equation has another final strength: Sexual dysfunctions can be seen as an early biomarker of NCDs, and lifestyle is often connected to STI risk. Moreover, sexual health has the intrinsic ability to motivate patients to improve their lifestyles. For all these reasons, infection and inflammation are a central clinical interest in the field of sexual medicine.

## Author contributions

F.F. and E.C. contributed equally.

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## Conflicts of interest

None declared.

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