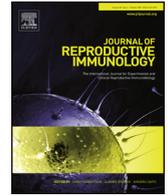




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Prostatitis and male infertility

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ABSTRACT

The prostate gland plays an important role in male reproduction. Inflammation of the prostate gland (prostatitis) is a common health problem affecting many young and middle aged men. Prostatitis is considered a correctable cause of male infertility, but the pathophysiology and appropriate treatment options of prostatitis in male infertility remain unclear. This literature review will focus on current data regarding prostatitis and its impact on male infertility.

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1. Introduction

Infertility is a common clinical problem, with 15% of couples unable to conceive with regular unprotected intercourse over a one-year period (World Health Organization, 1991). The etiology of infertility can be multifactorial. Twenty percent of infertility cases are secondary to male factor alone and 50% of all infertility cases have a male factor component (Dohle et al., 2005).

Male genital tract infections are an important and correctable etiology of male infertility. Up to 12% of male infertility cases are caused by male genital tract infections, including prostatitis, epididymitis, and orchitis (Dohle, 2003). Prostatitis is one of the most common healthcare problems in urology practice. It is considered among the most poorly understood medical problems. Prostatitis has been linked with male infertility and treatment of prostatitis may restore male reproductive function.

2. Role of prostate gland in male reproduction

2.1. Prostate gland

The prostate gland is the largest male accessory genital gland, weighing approximately 20 g. It is located at the base of the bladder and surrounds the proximal portion of the urethra (Fig. 1). The prostate gland is composed of epithelial and stromal cells. Epithelial cells provide secretory function while stromal cells constitute the connective tissue cells within the prostate.

Both ejaculatory ducts open within the urethra at the posterior surface of the prostate gland (prostatic urethra).

2.2. Prostatic secretions

Normal human ejaculate volume ranges from 1.5 to 5 ml. Mature sperm (spermatozoa) represent a minimal amount of the total ejaculate volume. The main contribution to ejaculate volume is from the secretions of the sex accessory tissues including the seminal vesicles, prostate, and epididymis. Prostatic secretions contribute up to 30% of semen volume (Owen and Katz, 2005).

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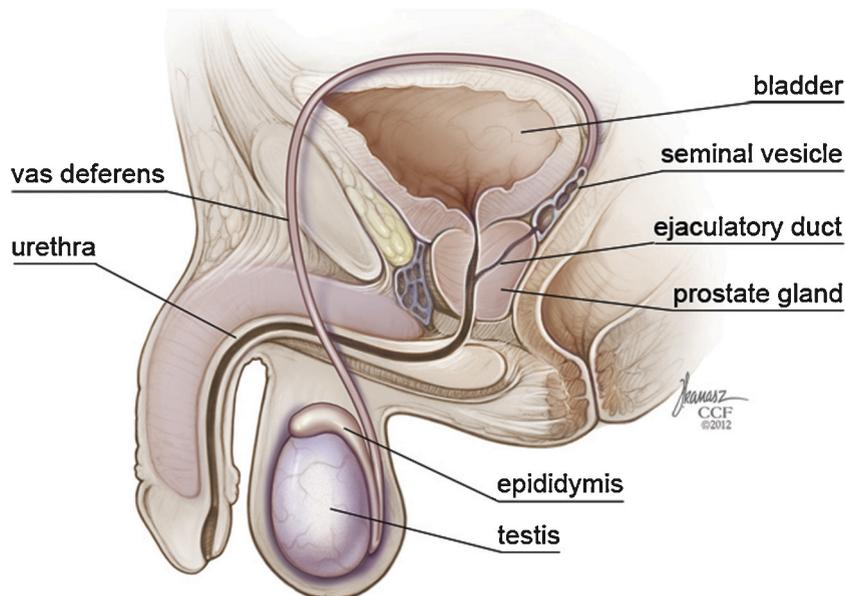


Fig. 1. The prostate gland and male genital organs.

During emission, the prostatic capsule and vas deferens simultaneously contract, secreting a homogeneous, serous, slightly acidic fluid (pH 6.8). This fluid contains a high amount of zinc, citric acid, calcium, phosphate, and other prostatic secretions important for sperm function (Marconi et al., 2009).

The highest concentration of zinc in the human body is in the prostate gland (Caldamone et al., 1979). At puberty, zinc concentration increases in men and reaches the maximum at 34–40 years of age (Bedwal and Bahuguna, 1994). Human sperm chromatin has a zinc-dependent stability at ejaculation (Bjorndahl and Kvist, 2011). Chromatin stabilization is affected when zinc is lost and DNA becomes vulnerable to factors that may lead to its fragmentation (Barratt et al., 2010). Zinc plays an essential role in male reproduction as an antimicrobial agent (Fair et al., 1976). Angiotensin converting enzyme (ACE) is associated with sperm development and deficiency of zinc may lead to ACE impairment and subsequent testosterone depletion, as well as decreased spermatogenesis (Bedwal and Bahuguna, 1994).

Citric acid is secreted by prostatic epithelial cells. It is available in prostatic secretions at high concentrations (Kavanagh, 1994). The seminal vesicle citric acid level is 100-fold less than the prostatic citric acid level (Zaneveld and Tauber, 1981). Citric acid plays an important role in prostatic function and maintains seminal pH (Said et al., 2009). High concentration of citric acid prevents coagulation of blood when mixed together with prostatic secretions (Zaneveld and Tauber, 1981).

Prostate specific antigen (PSA) is a member of the human kallikrein gene family and is secreted by the prostate gland into the seminal fluid at high concentrations. PSA functions in the liquefaction of seminal ejaculate to encourage sperm motility. PSA is elevated in the presence of many prostatic diseases, including inflammation,

malignancy, and benign prostatic hyperplasia (Nadler et al., 1995).

Prostatic fluid is rich in enzymes, sodium, potassium, and calcium (Zaneveld and Tauber, 1981). Prostatic profibrinolysin lyses the semen coagulum, leading to increased sperm motility (Huggins and Neal, 1942). This allows sperm progression within the female reproductive system and ultimately encourages fertilization and pregnancy.

In the prostate gland, free testosterone is converted by 5 α -reductase type 2 enzyme into dihydrotestosterone (DHT), a potent androgen that is 2–10 times more active than testosterone. Dihydrotestosterone (DHT) is necessary for male external genitalia growth.

3. Prostatitis

3.1. Definition and epidemiology of prostatitis

Prostatitis is considered the most common urological problem in men below 50 years of age (Collins et al., 1998) and the third most common urological diagnosis in men older than 50 years of age (Nickel, 1998). The overall lifetime prevalence of prostatitis is about 14% (Mehik et al., 2000). In the United States, approximately two million patients are diagnosed with prostatitis each year (Collins et al., 1998). About \$84 million was spent in the United States in 2002 on the treatment of prostatitis, excluding pharmaceutical costs, with health care dollars spent on prostatitis increasing with time (Pontari et al., 2007). The quality of life of many patients diagnosed with chronic prostatitis is significantly and negatively affected by the disease (Ahn et al., 2012).

3.2. Pathogens

The predominant pathogens in bacterial prostatitis are Gram-negative bacilli, mainly *Escherichia coli*, which is

isolated in prostatic secretions in up to 80% of prostatitis patients (Weidner et al., 1999a). Gram-positive *enterococci* are considered the second most common pathogens in prostatitis (Sharp et al., 2010). Other pathogens such as *Klebsiella* species, *Pseudomonas aeruginosa*, *Proteus mirabilis*, and *Enterobacter aerogenes* have been isolated in prostatitis cases. The role of *Chlamydia trachomatis* in chronic prostatitis is controversial. Mazzoli et al. (2010) found a high prevalence of *C. trachomatis* in chronic prostatitis (39.1%). In a study by Shortliffe et al. (1992) *C. trachomatis* was detected in patients with chronic prostatitis, but antichlamydial antibody titers were also detected in 20% of patients with nonbacterial prostatitis (NBP). In patients with acquired immune deficiency disease (AIDS) or with human immunodeficiency virus (HIV) infection, *Mycobacterium tuberculosis* and *Candida* species can be causative organisms (Ludwig et al., 2008).

3.3. Prostatitis categories and diagnosis

The US National Institute of Health, National Institute of Diabetes and Digestive and Kidney Diseases (NIH-NIDDK) proposed a categorization system for prostatitis. This system was designed to better define and understand prostatitis, including four categories: Category I (acute bacterial prostatitis), Category II (chronic bacterial prostatitis), Category III (chronic pelvic pain syndrome), and Category IV (asymptomatic inflammatory prostatitis) (Krieger et al., 1999) (Table 1). These categories are currently used in clinical practice to define the different types of prostatitis.

Clinical presentation may vary from asymptomatic inflammation to severe urological symptoms (Table 1). Men with acute prostatitis (Category I) usually present with acute pain in the genitorectal area and lower urinary tract symptoms (LUTS). These symptoms include frequency, dysuria, urgency, and obstructive urinary symptoms. Patients may also present with fever, shock or signs of multiorgan failure.

In chronic bacterial prostatitis (Category II), symptoms vary, from mild dysuria and urinary symptoms to hematospermia, vague pelvic pain, and erectile dysfunction. History of recurrent urinary tract infections caused by the same organism is a feature of chronic bacterial prostatitis.

The presentation of chronic pelvic pain syndrome (Category III) is similar to those of Category (II), but the main symptom in this category is chronic pelvic pain for at least 3 months. It is usually intermittent, vague, and located at the perineum, testes, penis, or lower abdomen. Patients with Category IV prostatitis are asymptomatic.

Urogenital examination is usually unremarkable except during acute infection, when the prostate is swollen, warm, firm, and tender during digital rectal examination. It is not recommended to perform a digital rectal examination in these patients owing to subsequent severe pain during examination and the risk of bacteremia.

Urine analysis and culture are required for any patient with suspected prostatitis. Semen culture is considered insufficient alone to diagnose chronic bacterial prostatitis since semen culture sensitivity is 45% (Zegarra Montes et al., 2008).

Prostate-specific antigen (PSA), urine cytology, cystoscopy, and other tests are optional and mainly used to exclude other important diseases that may cause similar symptoms such as prostate or bladder cancer (Nickel et al., 2002).

Expressed prostatic secretions are examined to localize the infection to the prostate by measuring the bacterial count from consecutive urine samples. Few urologists use this test routinely for their patients because of its high cost as well as false-positive and false-negative results (Moon, 1997; Nickel et al., 1998).

4. Mechanism of male infertility in prostatitis

4.1. Prostatic secretory dysfunction

The volume of prostatic secretions is known to diminish during male sex gland infections (Weidner et al., 1999b). Prostatitis has been linked with decreased prostatic excretory function, including decreases in citric acid, alpha glucosidase, fructose, and zinc secretions (Marconi et al., 2009). These factors play significant roles in prostate function, from enzyme activity to sperm motility. Although decreased semen volume can negatively affect male infertility, the mechanism of glandular secretory dysfunction in prostatitis and the effects of lower concentrations of prostatic enzymes and trace elements remain unclear.

4.2. Inflammatory mediators

Antisperm antibodies (ASAs) have been postulated to form with chronic urogenital infection or inflammation. Jarow et al. (1990) found an increased prevalence of ASAs in men with a history of nonbacterial prostatitis compared with controls. However, recent studies have challenged the suggestion of prostatitis-induced antisperm antibodies against human sperm. Marconi et al. (2009) studied 59 men with chronic prostatitis and did not find an association between prostatitis and ASAs. Another study by Hoover and Naz (2012) confirmed this. The authors evaluated 20 men with chronic prostatitis and did not find an association between chronic prostatitis and ASAs. Ultimately, recent evidence does not support ASAs secondary to prostatitis as an etiology of male infertility, but the true role of ASAs in prostatitis remains controversial.

Cytokines may play a role in prostatitis and male infertility. Cytokines released in response to local tissue stimulation, providing an early and important component of the innate host defense against infection (Oppenheim and Feldmann, 2000). Inflammation secondary to male prostatitis may promote an autoimmune response and subsequent imbalance of pro- and anti-oxidative factors within male semen, leading to deleterious effects on semen quality and sperm function (Fraczek and Kurpisz, 2007). Cytokines play a significant role in cell signaling and general biological functions, including cell growth, proliferation and modulation of inflammatory reactions. Multiple cytokines have been implicated in male infertility. Elevated seminal IL-1 β , IL-6, IL-8, IL-12, IL-18, TNF- α have all been linked with poor semen quality, ranging from decreased count and progressive sperm motility to increased

Table 1

Categories of prostatitis with main features.

Category	%	Etiological factors	Features
Category I Acute bacterial prostatitis	1–5%	<ul style="list-style-type: none"> • <i>E. Coli</i> (common) • <i>Enterococcus</i> • <i>Klebsiella</i> • <i>Pseudomonas</i> 	<ul style="list-style-type: none"> • Acute infection of the prostate gland • Fever, chills • Urinary symptoms • Pelvic or genital pain
Category II Chronic bacterial prostatitis	5–10%	Same as for Category I	<ul style="list-style-type: none"> • Recurrent infection of the prostate • Urinary symptoms • Pelvic or genital pain • Hematospermia
Category IIIA Inflammatory chronic pelvic pain syndrome	40–65%	Unknown	<ul style="list-style-type: none"> • Pelvic or genital pain for at least 3 months • Leukocytes in semen, expressed prostatic secretions, and post-prostatic massage secretions
Category IIIB Non-inflammatory chronic pelvic pain syndrome	20–40%	Unknown	<ul style="list-style-type: none"> • Pelvic or genital pain for at least 3 months • No leukocytes in semen, expressed prostatic secretions, and post-prostatic massage secretions
Category IV Asymptomatic inflammatory prostatitis	Unknown	Unknown	<ul style="list-style-type: none"> • No symptoms • Detected either by prostatic biopsy or by presence of leukocytes in the semen or expressed prostatic secretions during evaluation for other disease

Adopted from the [Canadian Guidelines on Sexually Transmitted Infections \(2008\)](#) – Public Health Agency of Canada – January 2008.

oxidative stress ([Motrich et al., 2005](#); [Martinez-Prado and Bermudez, 2010](#)). The type of seminal pro-inflammatory cytokine predominant in infertile males is dependent on the presence or absence of either leukocytes or pathogens ([Martinez-Prado and Bermudez, 2010](#)). Since current data have shown an increase in seminal fluid cytokine concentration irrespective of the presence or absence of leukocytes, prostatic tissues likely contribute a significant amount of cytokines measured in these studies. Further studies investigating cytokines in chronic prostatitis are necessary to fully elucidate the role of cytokines in prostatitis and male infertility.

4.3. Oxidative stress

Oxidative stress has been associated with prostatitis and male infertility ([Kullisaar et al., 2012](#)). Oxidative stress is defined by an excess of reactive oxygen species (ROS) coupled with decreased total antioxidant capacity. Seminal ROS are thought to originate predominantly from leukocytes and partially from sperm themselves. ROS produced by leukocytes in response to stimuli such as infection or inflammation ([Pasqualotto et al., 2000](#)). High levels of reactive oxygen species can lead to damage of cell membranes, intracellular proteins, organelles, and sperm DNA ([Ochsendorf, 1999](#)). ROS produced by activated seminal leukocytes during genitourinary inflammation have been correlated with impairment of sperm motility and metabolism ([Armstrong et al., 1999](#)). In addition, increased oxidative stress affects the sperm chromatin integrity and may lead to sperm DNA damage ([Aitken and Krausz, 2001](#)). Increased ROS levels are associated with leukocytospermia ([Sharma et al., 2001](#)). [Pasqualotto et al. \(2000\)](#) studied 36 men with chronic prostatitis and found an increase in seminal ROS and decreased seminal total antioxidant capacity. These ROS are usually scavenged by antioxidants (vitamins C and E, superoxide dismutase, etc.) but decreased concentrations of antioxidants may leave a surplus of ROS, resulting in further cellular damage ([Potts and Pasqualotto, 2003](#)).

4.4. Effects of pathogens

Multiple pathogens have been studied in chronic prostatitis, but most studies have been done with *E. coli*. *E. coli* has been shown to inhibit sperm motility and viability both directly and through soluble factors ([Diemer et al., 2000](#); [Schulz et al., 2010](#)). Electron microscopic investigation of *E. coli*-infected semen revealed sperm with structural damage to the mid-piece and tail, both important in sperm motility ([Diemer et al., 2000](#)). *E. coli*-induced damage to the acrosome was also noted, which would potentially impair acrosomal function and overall fertilization. Recently, [Fraczek et al. \(2012\)](#) observed mitochondrial changes and sperm membrane alterations when there is direct contact between sperm cells and *E. coli*, resulting in decreased sperm viability and fertilization potential.

Chlamydia trachomatis has also been directly associated with decreased sperm motility as well as abnormal sperm concentration and morphology ([Eley et al., 2005](#); [Mazzoli et al., 2010](#)). *C. trachomatis*-induced spermatozoa death is also well described and caused by lipopolysaccharide (LPS), which is 500 times more active than *E. coli* LPS isolates ([Hosseinzadeh et al., 2003](#); [Eley et al., 2005](#)). Thus, chronic *chlamydial* infection with secretion of small aliquots of LPS may have a significant impact on male spermatozoa and subsequent fertility over time.

Other pathogens, including *mycoplasma*, *ureaplasma*, and *enterococci* may play a role in prostatitis and male infertility. Further studies are required to delineate the clinical significance of these infective pathogens and a potential mechanism of action in male subfertility.

4.5. Ejaculatory dysfunction

Ejaculatory dysfunction may also occur secondary to prostatitis, leading to male infertility. Sexual dysfunction, which includes ejaculatory and erectile dysfunction, has been well linked to prostatitis ([La Vignera et al., 2012b](#)). Prostatitis is a known cause of premature ejaculation, with treatment of prostatitis leading to amelioration of

premature ejaculation (Zohdy, 2009). Although studies are limited, treatment of prostatitis may improve ejaculatory dysfunction and other concomitant adverse sexual symptoms.

5. Semen parameters in men with prostatitis

The impact of prostatitis on semen parameters remains controversial.

Male reproductive tract bacterial infections including chronic bacterial prostatitis (Category II) have been shown to negatively affect sperm quality (Marconi et al., 2009). In multiple studies, chronic non-bacterial prostatitis (Category III) has been proven to have a negative impact on sperm morphology as well as on sperm motility (Leib et al., 1994; Menkveld et al., 2003).

In contrast, other studies did not reveal any difference in standard sperm parameters such as semen concentration, sperm motility, and sperm morphology when prostatitis patients were compared with controls (Pasqualotto et al., 2000; Ludwig et al., 2003).

Alterations in semen parameters may also be secondary to the autoimmune response against prostate antigens. Motrich et al. (2005) demonstrated semen quality parameter alterations in chronic prostatitis patients with cellular autoimmune response. Overall, autoimmunity appears to play a role in prostatitis and poor semen quality, but the mechanism of action remains unclear.

Acrosomal functionality is also significantly affected in patients with chronic pelvic pain syndrome. Henkel et al. (2006) evaluated the effect of chronic pelvic pain syndrome (NIH IIIA and NIH IIIB) on different sperm parameters and on sperm acrosome reaction (AR), a measure of sperm head function. There was no difference in the sperm parameters between the two subcategories of the chronic pelvic pain syndrome (IIIA vs. IIIB). Sperm count and normal morphology were significantly lower in the patient groups compared with the controls. Total motility was significantly lower in the control group, but there was no difference in sperm progressive motility.

Recently, a large study evaluated bacteriospermia, elevated seminal leukocytes (ESL), and semen parameters in more than 4900 non-azoospermic subfertile patients (Domes et al., 2012). Elevated seminal leukocytes (ESL) alone were associated with poor semen parameters and a significant deterioration in sperm concentration, motility, morphology, and DNA fragmentation index. Patients with bacteriospermia alone (without ESL) had a statistically significant increase in DNA fragmentation index only. The authors concluded that the ESL is a dominant factor in deterioration of sperm parameters. This study was limited by the use of a modified definition for the ESL (≥ 1 PMN/100 sperm) and they did not use the standard WHO leukocytospermia definition ($>1 \times 10^6$ leukocytes/ml) (Domes et al., 2012). In a similar study, increased seminal leukocytes in the ejaculate of patients with chronic pelvic pain syndrome did not affect semen parameters (Ludwig et al., 2003).

Semen viscosity may also be increased in infertile patients with male accessory gland infection (La Vignera et al., 2012a). This increase in semen viscosity may

adversely affect semen parameters, especially sperm motility (Elia et al., 2009).

6. Treatment of prostatitis-related male infertility

Prostatitis is a frustrating healthcare problem for patients and clinicians. There is a paucity of studies investigating the treatment of prostatitis-related male infertility. Generally, bacterial prostatitis should be treated with appropriate antibiotic therapy. This may subsequently improve male fertility and overall sexual dysfunction. Antibiotic treatment of men with prostatitis and the resultant premature ejaculation can improve intravaginal ejaculatory latency time, a measure used to quantify the severity of premature ejaculation (Zohdy, 2009). Hamada et al. (2011) reported significant improvement in natural pregnancy rates in infertile patients with low-level leukocytospermia (0.2×10^6 – 1.0×10^6 leukocytes/ml) after a 3-week course of oral doxycycline antibiotic.

Antioxidants may play a role in improving male fertility. Treatment of chronic prostatitis may be responsive to antioxidant therapy. Lombardo et al. (2012) treated men with chronic prostatitis with antioxidants for 6 months and noted a statistically significant decrease in seminal fluid leukocytes, improved sperm motility, and improvement in pain scores.

Given the association of increased ROS in subfertile men with prostatitis, antioxidants may prove beneficial in this patient population (Pasqualotto et al., 2000). Carnitines have also been shown to be efficacious in abacterial prostatitis, leading to a reduction in semen ROS and improvement in sperm motility, viability, and pregnancy rates (Vicari et al., 2002). Overall, further studies using alternative treatments for prostatitis, including anti-inflammatory medications, herbal therapies and holistic modalities may prove efficacious in subfertile men with prostatitis.

7. Assisted reproductive technique outcomes

The deleterious effect of leukocytospermia on sperm function has been well established in past studies. Barraud-Lange et al. (2011) assessed the effect of leukocytospermia on assisted reproductive technique (ART) outcomes when he distributed retrieved eggs among three groups of sperm extracted from varied levels of seminal fluid leukocytes. Results surprisingly showed that leukocytospermia was associated with improved fertilization and clinical pregnancy rates, irrespective of the level of leukocytospermia. Mean gestational age and infant weight were also improved in leukocytospermia groups. Intracytoplasmic injection (ICSI) was required more often in the leukocytospermia groups than in the non-leukocytospermic patients group. Moderate leukocytospermia ($\leq 10^6$ ml⁻¹) appears to have a beneficial effect by improving the fertilization and pregnancy outcome after ART.

In contrast, high leukocytospermia ($>10^6$ ml⁻¹) was associated with increased rates of early pregnancy loss and ectopic pregnancy. This negative effect of leukocytospermia on ICSI outcomes supports findings in previous studies (Yilmaz et al., 2005). However, Lackner et al. (2008) also investigated the fertilization and pregnancy rate from

leukocytospermia samples used in ART and did not find that leukocytospermia had an effect on ART outcomes (IVF or ICSI). Ultimately, the relationship between leukocytospermia and ART remains unclear. Further studies are required to delineate the effects of leukocytospermia on ART outcomes and its pathophysiology.

Sperm DNA damage is reported to be more than double in the presence of leukocytospermia compared with non-leukocytospermic semen samples (Erenpreiss et al., 2002). Selection of fragmented DNA spermatozoa for ART is associated with poor results in intracytoplasmic injection (ICSI) (Lopes et al., 1998) and in vitro fertilization (IVF) (Sun et al., 1997).

8. Conclusion

Prostatitis is a common health condition characterized by a collection of symptoms and signs secondary to inflammation of the prostate gland and affecting mostly middle-aged men with considerable morbidity. Patients with prostatitis are usually frustrated owing to the natural history of the disease. The diagnosis of prostatitis is mainly by exclusion of other conditions and the treatment options are usually noncurative.

Prostatitis is recognized as one of the causes of male infertility and several studies have shown that it has an impact on fertility potentials through multiple and poorly defined mechanisms. It may also affect the outcome of assisted reproductive therapy. There is a need for more studies to understand the pathogenesis of prostatitis, elucidate the negative impact of prostatitis on male fertility (e.g., sperm DNA integrity and apoptosis), improve the diagnostic criteria, and focus on the efficacy of various treatment modalities, such as the antimicrobials, anti-inflammatory agents, and the antioxidants.

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