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Male accessory gland infection (MAGI): Over-diagnosed or under treated in infertile men?

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ABSTRACT

Male accessory gland infection (MAGI) is a significant yet often under-recognized contributor to male infertility. This review article provides a comprehensive synopsis of MAGI, distinguishing it from male genital tract infection (MGTI) and emphasizing the challenges posed by asymptomatic cases. It concisely presents the pathophysiology of MAGI, highlighting the inflammatory response characterized by leukocyte infiltration, elevated pro-inflammatory cytokines, and increased production of reactive oxygen species, which collectively impair sperm quality and fertilizing capability. The article discusses the complexities in diagnosis due to the overlap with benign conditions and presents emerging diagnostic markers. It also critically reviews the controversies surrounding the over-diagnosis and under-treatment of MAGI, emphasizing the need for improved diagnostic accuracy to encourage appropriate treatment. Current therapeutic strategies are explored, revealing variable efficacy and the importance of personalized approaches. This review aims to provide a clear understanding of the clinical implications of MAGI and to guide accurate diagnosis and effective treatment, ensuring better fertility outcomes for affected patients.

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Introduction

Male accessory gland infection (MAGI) refers to inflammatory disorders of the male accessory sexual glands, including the seminal vesicles, prostate, and bulbourethral glands, as initially defined by Comhaire and colleagues [1]. MAGI constitutes a nosological category implicated in male infertility, exhibiting a prevalence of 2% to 18% among patients with infertility issues [2], that may be influenced by the presence of underlying diseases [3]. Chronicity and recurrence are notable features of MAGI, making its management challenging for clinicians [4].

The concept of MAGI has evolved significantly since its initial description, reflecting advancements in medical diagnostics and a deeper understanding of male reproductive health [4–6]. Over time, the definition of MAGI has expanded to include asymptomatic cases, recognized through the advent of more sophisticated diagnostic tools such as transrectal ultrasonography and molecular testing [7,8]. Although recent studies have not established a consistent link between leukocytospermia (LCS) and genital tract infections, the World Health Organization (WHO) recognizes LCS as a diagnostic criterion for MAGI, emphasizing its importance along with other sperm parameters for diagnostic confirmation [9,10].

While existing reviews have extensively discussed the clinical presentation, diagnosis, and general treatment strategies for MAGI, they often lack a comprehensive analysis of emerging diagnostic advancements and the nuances of managing asymptomatic cases, which are increasingly identified through improved diagnostic modalities [11,12]. Previous literature has primarily focused on symptomatic cases and generalized approaches, leaving a gap in understanding how to navigate the complexities associated with asymptomatic presentations and their implications for male fertility. Furthermore, the differentiation between MAGI and male genital tract infection (MGTI) has been addressed inconsistently, leading to potential overlaps in treatment approaches that may compromise patient outcomes [5,8]. This review intends to fill this gap by providing an in-depth exploration of asymptomatic MAGI, clarifying its distinctions from MGTI, and examining the latest evidence surrounding its management, including the impact on reproductive health. By addressing these underexplored areas, this review aims to contribute to more nuanced clinical guidelines and enhance the precision of diagnostic and therapeutic approaches for MAGI.

Pathophysiology of MAGI and MGTI

MAGI and MGTI represent significant yet often underdiscussed areas of male reproductive health, particularly in the context of their pathophysiology and

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impact on fertility [2,4]. It is crucial to explore the critical dynamics of leukocyte behavior in response to these conditions, the direct tissue damage induced by various pathogens, and the intricate interplay between infection and reproductive function (Figure 1).

Leukocyte dynamics in the male genital tract

MAGI encompass infection or inflammation of the accessory glands such as the prostate, seminal vesicles, and Cowper's glands. This differs from MGTI which involve the entire genital tract, affecting both the glands and ducts, often causing inflammation [5]. The presence of LCS and/or pathogens in semen, along with signs of inflammation in the male genital tract, are key indicators of MGTI. Inflammation in the excurrent duct system, which is neither part of the male reproductive system nor classified as accessory glands, is not included in the original definition of MAGI. Given the challenges in differentiating between distinct localized infections [13], the broader term MGTI was introduced to encompass the entire male reproductive tract [14]. While seminal leukocyte concentration alone has limited diagnostic value, higher concentrations of seminal polymorphonuclear neutrophils (PMN), granulocyte elastase (≥230 ng/mL), and elevated pro-inflammatory cytokines, such as interleukin (IL)-6 and IL-8, offer more precise diagnostic and management tools for MAGI [2,15].

Leukocytes in semen include granulocytes (primarily PMNs), macrophages, and lymphocytes. PMNs, originating mainly from the prostate and seminal vesicles, comprise around 50–60% of seminal leukocyte concentration [16,17]. LCS, defined as seminal leukocytes above 1 million/mL, is a useful diagnostic parameter for infections or inflammation in the male genital tract, whether MAGI or MGTI [10].

Leukocytes play a critical role in the inflammatory response, synthesizing cytokines and pro-inflammatory mediators, including nitric oxide, prostaglandins, and chemokines [17]. Through this response, cytokines facilitate pathogen elimination and promote the apoptosis of abnormal spermatozoa via phagocytosis and reactive oxygen species (ROS) generation [16].

In cases of elevated leukocytes, as seen in MAGI, inflammatory cytokines such as interleukin-6 (IL-6) and interleukin-8 (IL-8) are released. These cytokines intensify inflammation and lead to excessive ROS production, causing oxidative stress (OS) that adversely affects sperm quality. Leukocytes, when activated, produce up to 1,000 times more ROS than spermatozoa, significantly contributing to increasing OS in semen [18,19]. This heightened OS impairs sperm function by damaging the sperm membrane, altering motility, and increasing DNA fragmentation, which ultimately compromises sperm quality and fertilizing potential. Additionally, the inflammatory environment can obstruct the seminal tract, further impacting semen quality and potentially leading to infertility [5].

In MGTI, infections are typically more generalized, affecting multiple parts of the genital tract. For instance, pathogens such as Chlamydia trachomatis (c. Trachomatis), Ureaplasma urealyticum

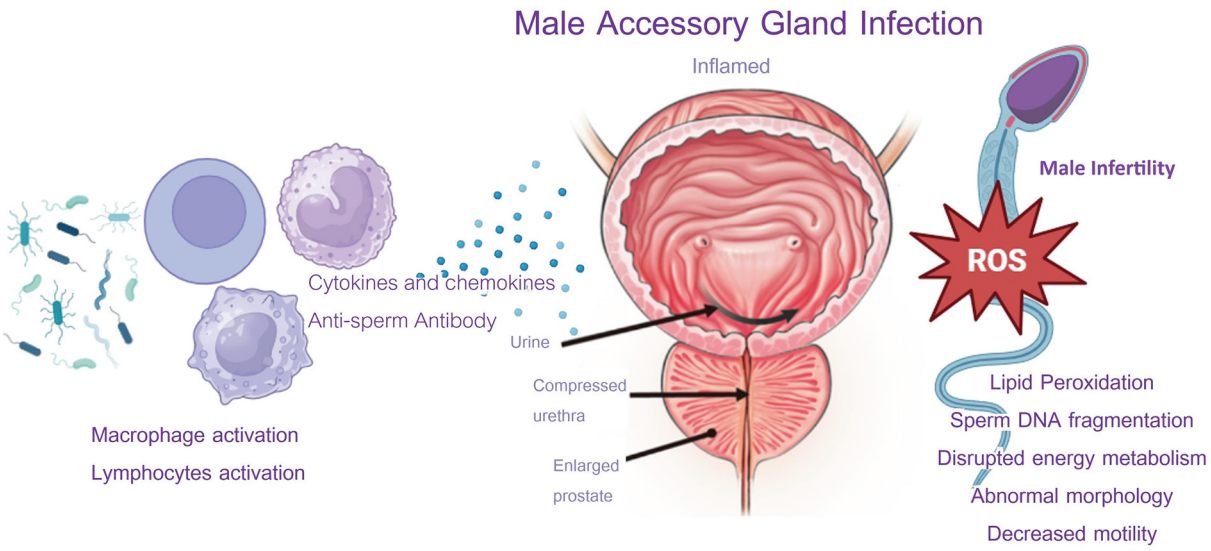

Figure 1. Comprehensive overview of how male accessory gland infection (MAGI) can impair fertility by disrupting sperm function. MAGI caused by bacteria or other pathogens lead to inflammatory responses. It involves macrophage and lymphocyte activation, which triggers the release of cytokines and chemokines, as well as the production of anti-sperm antibodies. Additionally, leukocytes infiltrate the glandular tissue, exacerbating the inflammatory response. Collectively, these processes promote excess generation of reactive oxygen species (ROS), which damage sperm by causing lipid peroxidation, DNA fragmentation, and disrupted energy metabolism. The cascade of immune responses and oxidative stress ultimately manifests as male infertility, characterized by sperm with abnormal morphology and decreased motility. Thus, the diagram provides a detailed understanding of the immune-mediated and oxidative mechanisms that link prostate infection to impaired sperm quality and fertility.

(U. urealyticum), Neisseria gonorrhoeae (N. gonorrhoeae), and Escherichia coli (E. coli), can cause widespread inflammation, with leukocyte accumulation leading to deteriorating spermatogenesis and ROS-mediated sperm damage [5,15].

However, LCS alone does not have the specificity to precisely localize the infection to either the accessory glands (as in MAGI) or other parts of the genital tract (as in MGTI). To further differentiate between MAGI and MGTI, additional diagnostic markers are needed. These include seminal granulocyte elastase and cytokine levels [5,15].

Pathogen-induced male reproductive disruptions

The male reproductive system is susceptible to infections from various pathogens, including bacteria, viruses, and fungi, which can damage key tissues. This vulnerability stems from the shared passages between the reproductive and urinary tracts, which provide entry points for infections. Additionally, the reproductive system's warm, moist environment, high blood flow, and glandular secretions promote microbial growth. The immune privilege of the testes, while protective for germ cells, can also allow infections to persist [20].

Pathogens that infect the male reproductive system often remain asymptomatic, leading to chronic and undetected infections that can adversely affect reproductive health and fertility [21]. These infections, etiological factors of MAGI and MGTI, impair spermatogenesis and sperm function. Over time, chronic infections can further damage reproductive tissues, leading to infertility and chronic pain.

Prominent pathogens associated with reproductive infections include C. trachomatis, U. urealyticum, N. gonorrhoeae, Mycoplasma hominis, and Mycoplasma genitalium (M. genitalium), all of which are sexually transmitted [22]. Additionally, E. coli accounts for 65–80% of cases of epididymo-orchitis and prostatitis, which can result in impaired sperm function and asymptomatic inflammation [22,23]. These pathogens elicit acute inflammatory responses, disrupt spermatogenesis, and increase ROS production, which can further harm spermatozoa [24].

Asymptomatic infections are common, with approximately 50% of male patients with MGTI unaware of their condition, thus posing risks for infertility and unintentional transmission [22,25–27]. Elevated ROS production and diminished scavenger properties are often observed in asymptomatic cases, where antibiotic treatment has shown to improve semen quality [5,28].

Pathogens such as C. trachomatis, U. urealyticum, Mycoplasmas, and members of the Enterobacteriaceae family are detectable through PCR or microbial cultures [29]. Studies have demonstrated that infections with E coli, Staphylococcus aureus, U. urealyticum, and M. hominis negatively impact sperm parameters, including count, motility, and mitochondrial membrane potential. However, the relationship between these infections and semen quality remains inconsistent across studies [30–34].

Infections in the genital tract can disrupt the hormonal balance necessary for normal reproductive functions by triggering inflammatory cytokines that interfere with the hypothalamic-pituitary-gonadal (HPG) axis, leading to reduced secretion of luteinizing hormone and follicle-stimulating hormone, ultimately lowering testosterone levels and impairing spermatogenesis. Additionally, infections increase OS, damaging Leydig and Sertoli cells, which are crucial for hormone production and sperm maturation. Certain pathogens may also directly invade testicular tissue, causing cellular damage, while chronic infections can provoke autoimmune responses against germ cells, further compromising hormonal function and fertility [35]. Understanding the pathophysiology of MAGI, particularly the hormonal disruption and immune responses involved, is therefore essential to formulating effective treatment strategies and improving diagnostic accuracy.

Differentiation between MAGI and MGTI

Both MAGI and MGTI are significant causes of male infertility contributing to around 15% of infertility cases. Unfortunately, nearly half of them are asymptomatic. It is not uncommon for this disease to become a silent disease that increases the risk of infecting the partner through sexual intercourse, resulting in infertility for both the parties [37,38].

The most fundamental difference between MAGI and MGTI is the anatomical location of the infection process. MAGI is an infection that occurs in the male accessory glands (epididymis, seminal vesicles, prostate, and bulbourethral glands), while MGTI involves infections in the genital tract. Therefore, in MAGI, the infection is localized, whereas in MGTI, it is more widespread. Although they have differences, they can be interrelated. The occurrence of MGTI can negatively impact seminal plasma, leading to reduced semen volume and decreased levels of alpha-glucosidase, fructose, and zinc. These reductions, which reflect impaired secretion capacity of the male accessory glands, may serve as markers for both MGTI and MAGI [37,39]. (Table 1).

The most common causes of epididymitis are infections of C. trachomatis, E. coli, and N. gonorrhoeae. Additionally, it can also be caused by Mycobacterium tuberculosis, Candida spp, Brucella, and Mumps virus. Prostatitis is most often caused by Trichomonas vaginalis, C. trachomatis, E. coli, and U. urealyticum.

Table 1. Differentiation between male accessory gland infection (MAGI) and male genital tract infection (MGTI).

Characteristics	MAGI (Male Accessory Gland Infection)	MGTI (Male Genital Tract Infection)
Anatomical Sites Affected	Accessory glands (seminal vesicles, prostate, bulbourethral glands)	Entire genital tract, including accessory glands, urethra, penis, epididymis, and testes
Location of Infection	Localized, typically confined to the accessory glands	Widespread, involving multiple genital tract structures
Common Causative Pathogens	*Chlamydia trachomatis* *Escherichia coli* *Neisseria gonorrhoeae* *Mycoplasma hominis* *Candida spp.* *Mumps virus*	*Neisseria gonorrhoeae* *Chlamydia trachomatis* *Mycoplasma genitalium* *Ureaplasma urealyticum* *Escherichia coli*
Mechanisms of Pathophysiology	Inflammatory response primarily in accessory glands causing local tissue damage, increased oxidative stress Immune-mediated disruption of local environment, impacting seminal quality Cytokine release interferes with hormone regulation and spermatogenesis in localized regions	Inflammatory response in broader genital tract leading to more widespread tissue damage Higher potential for systemic immune response due to widespread infection Greater potential for direct immune cell invasion due to broader tissue involvement
Symptoms	Often asymptomatic; may cause mild pelvic pain, ejaculatory discomfort Chronic cases may lead to infertility due to impaired spermatogenesis	Can be symptomatic or asymptomatic; may present with discharge, pain, and swelling Symptoms often more pronounced, with pain and systemic signs such as fever
Diagnostic Tools	Semen analysis for leukocytospermia (LCS), high ROS, and decreased sperm motility and morphology Seminal fluid culture to identify pathogens like *E. coli*, *Chlamydia*, *Mycoplasma*, and others PCR and molecular testing for pathogen-specific DNA (e.g. *Chlamydia*, *Ureaplasma*) Transrectal ultrasound (TRUS) for structural abnormalities in accessory glands	Semen analysis to detect pathogens, especially for cases with urethritis and urethral discharge Urine culture and urethral swab culture for urethral pathogens PCR for broader range of pathogens commonly affecting the entire genital tract Ultrasonography for detecting inflammation across multiple genital sites (epididymis, testes)
Treatment Considerations	Targeted antibiotics to reduce inflammation and eradicate pathogens in accessory glands Antioxidants to manage oxidative stress	Broader-spectrum antibiotics due to varied sites and pathogens Management of broader inflammation and potential systemic symptoms
Potential Complications	Chronic inflammation and scarring within accessory glands, potentially impairing fertility	Infertility due to damage across multiple genital sites; possible systemic spread of infection

Meanwhile, the most common cause of urethritis is N. gonorrhoeae (in the gonococcal type) or C. trachomatis, M. genitalium, U. urealyticum (in the non-gonococcal type) [37].

Several causes of MAGI include bacterial and non-bacterial factors [4,40]:

(a) Bacterial MAGI- If more than 10^3 pathogenic bacteria or $>10^4$ non-pathogenic bacteria per ml of seminal fluid culture are found.
(b) Non-bacterial MAGI- If only clinical symptoms are found along with findings on ultrasound (such as prostatitis, prostate-vasculitis, or prostate-vesiculo-epididymitis).

The diagnosis begins with a medical history, where a history of urinary tract infection or sexually transmitted infection is identified. This is followed by a specific medical history and physical examination according to the suspected anatomical location. For example, in epididymitis, there will be pain and warmth in the epididymis accompanied by fever. In prostatitis, the typical symptoms include pain or discomfort during urination accompanied by pain or discomfort around the perianal area. Meanwhile, urethritis presents symptoms similar to prostatitis, such as dysuria, but is accompanied by purulent discharge and also urethral pruritus [37].

Based on laboratory findings, cases of MAGI typically exhibit abnormalities in semen analysis, especially in the macroscopic examination of seminal fluid. For example, an increase in pH, viscosity, and semen volume may be observed due to increased secretion from the male accessory glands. In severe infection conditions, the seminal fluid may appear greenish with a foul odor. Meanwhile, microscopic examination may reveal LCS [37,41].

Role of MAGI in male infertility

Studies report MAGI in 2%–18% of infertile patients [2], and it is recognized by the European Association of Urology as a contributing factor to infertility [42,43]. As already emphasized, the role of MAGI in male infertility has been contentious due to its frequently asymptomatic nature and variable diagnostic criteria [4]. The diagnostic criteria for MAGI, first proposed by Comhaire and colleagues in 1980, rely on clinical, biochemical, and microbiological evidence [1]. While initial studies questioned the relationship between LCS and confirmed infections, current guidelines identify LCS as a diagnostic marker [4,5].

MAGI impairs fertility through various mechanisms. Microorganisms can directly affect spermatogenesis and spermatozoa, triggering immune responses that disrupt testicular immune regulation [15]. For example, C. trachomatis has been linked to reduced conception

rates and detection of bacterial DNA in testicular tissue after epididymo-orchitis [44]. Pathogens may adhere to spermatozoa or release IL-8, reducing motility and fertilization capacity [45]. Anti-sperm antibodies (ASA) are observed in 20% of MAGI cases, though their significance remains uncertain [46,47]. This immunological assault on spermatozoa can reduce fertility potential and is considered a significant immunological barrier in some cases of male infertility. In addition, the OS and inflammation owing to MAGI can affect the HPG axis as discussed previously and impair male reproductive functions [35].

Excessive ROS production during infections leads to OS, disrupting sperm function and damaging protective seminal secretions [35,36]. Additionally, anatomical blockages in the seminal tract may result in azoospermia [48]. Patients with chronic bacterial prostatitis (CBP) and irritable bowel syndrome (IBS) show higher MAGI prevalence and greater sperm abnormalities than those with CBP alone [3]. Different bacterial strains uniquely impact sperm parameters, contributing to membrane damage, receptor dysfunction, and DNA fragmentation [26,31,33,46] E. coli reduces sperm count, motility, and morphology while increases ROS production [33]. Similarly, C. trachomatis and other pathogen can cause sperm DNA fragmentation and mitochondrial damage [26,31].

MAGI is implicated in reduced semen volume and altered biochemical markers like fructose and zinc, contributing to impaired sperm production [49]. This results in decreased fertility rates, confirmed by studies indicating lower conception after intrauterine insemination [50]. At higher levels of infection, MAGI or MGTI can cause scarring/fibrosis in the male reproductive tract, resulting in obstructive azoospermia.

Therapeutic interventions with antibiotics show varying efficacy; microbial forms of MAGI generally responding well, while inflammatory forms often require long-term anti-inflammatory treatment [51]. Despite treatment improvements, the persistence of inflammation remains a challenge, emphasizing the need for early detection and targeted therapy [2].

Diagnostic markers and methods for MAGI

In seminal fluid, besides spermatozoa, there are also epithelial cells and round cells. The former originate from the genitourinary tract, while the latter usually consists of a combination of immature germinal cells and leukocytes. LCS is a condition where there is an increase in the level of leukocytes in semen exceeding 1×10^6 per ml of semen. LCS is usually an early indication of MAGI, although the significance of the relationship between LCS and male fertility potential remains controversial, especially since 50% of MAGI cases are asymptomatic. The inflammatory response due to this infection typically involves TNF-α, IL-8, IL-6, and IL-1α [37,38,52–54].

There are three challenges encountered when making LCS the cornerstone for establishing the diagnosis of MAGI. Firstly, determining the lower limit of leukocytes (1×10^6 leucocytes/peroxidase positive cells per ml of semen) itself remains controversial and lacks a sufficiently strong evidence base [55]. On the other hand, the presence of low-level leukocytes ($0.2–1 \times 10^6$ leukocytes/ml) also has negative effects on semen parameters, and the therapeutic process for cases of low-level seminal leukocytes results in a significant pregnancy rate [52].

The second challenge lies in the examination to determine LCS (immunochemistry examination being the gold standard due to its high specificity). This examination is not a simple test to apply in daily clinical practice; it is time-consuming and requires a considerable cost. Therefore, the determination of LCS typically utilizes a simpler examination method, which is by counting peroxidase-positive cells using Ortho-toluidine or Endtz test. The last-mentioned examination is the most commonly used in andrology laboratories due to its simple and cost-effective nature. However, this does not mean it is without drawbacks. Both examinations utilize carcinogenic substances, so caution must be exercised during their execution [38,53]. While the Endtz test and other peroxidase tests are crucial in distinguishing leukocytes from other round cells in semen, with granulocytes staining positively [56], the test primarily identifies granulocytes and may not account for all white blood cells [57]. The gold standard immunochemistry methods using specific leukocyte antigens like CD45 and CD53 enable comprehensive leukocyte detection, providing clearer distinctions between MAGI and MGTI [5,57]. A combination of leukocyte count, specific antigen testing, and clinical assessments yields the most accurate differentiation between MAGI and MGTI, enabling targeted treatment approaches.

LCS is not always caused by infection. Several other causes can also manifest as LCS in clinical practice. One example is varicocele cases where higher leukocyte concentration is found in subfertile patients with varicocele compared to fertile men. A positive correlation is also found between LCS and male smokers, attributed to the inflammatory response to tobacco metabolites activating the influx of leukocytes into semen. In the case of men who have a history of spinal trauma (spinal cord injury), where it is estimated that LCS occurs in 60% of men who experience this history. In addition, marijuana users, heavy alcohol drinkers, and patients who are undergoing selective estrogen receptor modulator (SERM) drug therapy such as clomiphene citrate can also experience LCS [38,52].

Diagnostic imaging is helpful in in MAGI workups. Scrotal and prostate-vesicular ultrasound with an endorectal probe (TRUS) allows for identification of the localization of the inflammatory process which can be at the epididymal level (epididymitis), at the seminal vesicles

(vesiculitis), and/or at the prostate (prostatitis). TRUS can also be helpful to diagnose an obstructive pathology of the seminal tract caused by median cysts of the prostate or obstruction of the ejaculatory ducts. At a higher level, magnetic resonance imaging can be useful for identifying infections/abscesses in the accessory glands and distinguishing them from malignant neoplasms. Finally, polymerase chain reaction, a very sensitive and specific method, can also be used to diagnose cases of MAGI or MGTI. With its capabilities, PCR can detect particular DNA/RNA infections that cause these diseases quickly and accurately, although the cost limits its use.

Review of current treatment guidelines

The therapy in cases of MAGI aims to inhibit and stop the ongoing infection process. Subsequently, improvements in seminal plasma parameters are expected, and if possible, it may lead to the desired pregnancy. However, in some specific conditions, this process does not always proceed smoothly towards its ultimate goal. One of the reasons for this is that the infection has been ongoing for a long time, resulting in chronic inflammation [38,58].

Several therapeutic modalities that can be used in cases of MAGI (Table 2) include the use of antibiotics adjusted according to the results of microbial culture and antibiotic sensitivity tests (because providing therapy based solely on LCS has a low diagnostic value for detecting bacteriospermia), or empirical antibiotic use (such as doxycycline 100 mg once or twice a day for 28 days) as an initial step while awaiting culture results. To support antibiotic therapy, fibrinolytic drugs such as bromelain 160 mg/day) have shown good synergy in helping antibiotics to penetrate prostatic tissue [59–61]. Additionally, their proteolytic properties are beneficial in reducing the viscosity of seminal fluid caused by the inflammatory process. As anti-inflammatory agents, the use of drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) (salicylates, Cox-2 inhibitors, and profens) and steroidal anti-inflammatory drugs (glucocorticoids such as prednisolone) can also be considered. Excessive ROS production can occur in cases of MAGI, so the use of antioxidants also plays a role in combating the adverse effects of OS, which can increase sperm DNA damage, thereby reducing sperm ability to fertilize an egg. Finally, PDE-5 inhibitor drugs may also be an option to help improve sperm count and motility [4].

In severe situations of MAGI, such as obstructive azoospermia, TURED or vasoepididymostomy is used to open the obstruction. This therapeutic approach is not without risk because it may introduce additional difficulties in the presence of ASA. Furthermore, if this obstruction cannot be removed, assisted reproductive technique is the couple's last option for having children.

In summary, treatment for MAGI typically involves antibiotics aimed at symptom relief, microbial eradication, and reducing inflammation [62]. While this may improve sperm quality, no substantial evidence links MAGI treatment to increased conception rates. The presence of C. trachomatis and M. hominis in semen, even without symptoms, has been associated with reduced sperm quality, which appears to improve following antibiotic therapy. However, additional studies are needed to validate these observations [63]. Additional research is needed to evaluate whether combined antibiotic and antioxidant therapy benefits fertility outcomes in infertile men with LCS. The EAU guidelines recommend evaluating and treating sexual

Table 2. Treatment modalities of MAGI.

Types	Drugs
Antibiotics	Ciprofloxacin Levofloxacin Azithromycin Doxycycline clarithromycin
Nonsteroidal antiinflamatory	Salicylates Profen COX-2 inhibitors
Fibrinolytics	Serratiopeptidase Bromelain Escin
Antioxidants	Enzymatic • Superoxide Dismutase (SOD) • Catalase • Glutathione peroxidase Nonenzymatic • Glutathione • N-acetyl-cysteine (NAC) • Vitamins A, C, E • Co-Q 10 • Carnitines • Myoinositol • Lycopene • Astaxanthin
Steroidal antiinflammatory	Prednisolone
PDE-5 inhibitor	Tadalafil

partners for sexually transmitted infections in cases of MAGI, given the risk of transmission [43].

Debate on over-diagnosis and under-treatment

Critics of the current diagnostic approach to MAGI argue that the broad clinical criteria may lead to over-diagnosis. The diagnosis of MAGI often relies on a combination of symptomatic presentation, semen analysis, and ultrasound findings [2,11]. However, the specificity of these criteria is questioned, as the symptoms and imaging findings can overlap with other benign conditions such as benign prostatic hyperplasia and prostatitis [64].

Over-diagnosis could lead to unnecessary treatment, causing patients to undergo potentially harmful therapies, including prolonged courses of antibiotics and invasive procedures such as transrectal prostate biopsies, testicular biopsies, or seminal vesicle aspirations. These interventions not only carry risks such as infection, bleeding, and discomfort but may also detrimentally affect patients' quality of life while contributing to the growing problem of antibiotic resistance [65].

On the other side of the debate, the consequences of under-treatment of MAGI can be significant. Inadequate treatment of MAGI can lead to persistent infection, chronic pain/discomfort, and potentially irreversible damage to the accessory glands, which can significantly reduce male fertility [14]. The long-term consequences extend beyond physical health, with untreated chronic genital infections often causing psychological distress and straining interpersonal relationships due to infertility. This highlights the need for balanced diagnostic and therapeutic strategies. Achieving this balance requires a deeper understanding of MAGI pathophysiology and the development of more accurate diagnostic tools to minimize unnecessary treatments while ensuring timely and effective management [2,49].

Conclusion and future perspectives

MAGI remains a multifaceted and evolving entity in reproductive health, presenting significant challenges in diagnosis, management, and understanding its role in male infertility. Despite advancements in diagnostic criteria, including LCS, imaging techniques, and biochemical markers, there is still debate regarding over-diagnosis and under-treatment. Critics emphasize that broad clinical criteria may lead to unnecessary treatment, potentially causing adverse effects and contributing to antibiotic resistance. On the other hand, under-treatment could result in chronic inflammation, persistent infection, and irreversible glandular damage, further exacerbating infertility issues.

Current therapeutic regimens, such as antibiotics and anti-inflammatory agents, show promise but are not universally effective, particularly in chronic conditions or asymptomatic cases. Therefore, a more nuanced understanding of the pathophysiology of MAGI, including the interplay between infection, inflammation, and immune responses, is crucial for refining treatment strategies. Diagnostic tools like ultrasound and molecular markers should be further standardized to improve the detection and differentiation of MAGI subtypes.

Future research should focus on developing specific proteomic and genomic markers that can accurately differentiate microbial and inflammatory forms of MAGI. Emerging technologies, such as proteomic platforms and next-generation sequencing, offer the potential to identify unique biomarkers and understand the molecular mechanisms underlying inflammation and immune responses in MAGI. These insights could facilitate personalized treatment strategies, reducing unnecessary interventions and ensuring targeted therapy. Additionally, exploring the role of the male genital tract microbiome and its influence on immune regulation could reveal novel targets for treatment.

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