Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2026**; 31(11): 52686
https://doi.org/10.31083/FBL52686

Systematic Review

Role of Seminal Microbiota Dysbiosis and Inflammatory Cytokines in Male Infertility: A Systematic Review and *In Silico* Pathway Analysis

Ayoushna Panigrahi[1,†], Bhagyalaxmi Sahoo[1,†], Lipika Priyadarsini Patra[1], Ajaya Kumar Moharana[1], Ashutosh Sahu[1], Lisa Goutami[1], Jasmine Nayak[1], Suresh C Sikka[2], Luna Samanta[1,2], Manesh Kumar Panner Selvam[2,*], Soumya Ranjan Jena[1,*]

[1]Redox Biology & Proteomics Laboratory, Department of Zoology and Centre of Excellence for Environment and Public Health, Ravenshaw University, 753003 Cuttack, India
[2]Department of Urology, Tulane University School of Medicine, New Orleans, LA 70065, USA
*Correspondence: mpannerselvam@tulane.edu (Manesh Kumar Panner Selvam); srjenaa@gmail.com (Soumya Ranjan Jena)
[†]These authors contributed equally.
Academic Editor: Gianluca Paventi
Submitted: 8 April 2026 Revised: 21 June 2026 Accepted: 30 June 2026 Published: 18 November 2026

Abstract

Background: The seminal microbiota plays an important role in maintaining male reproductive health by supporting sperm function, immune homeostasis, and protection against pathogenic microorganisms. Emerging evidence suggests that dysbiosis of seminal microbiota may contribute to male infertility through the induction of an inflammatory response and increased production of pro-inflammatory cytokines. This systematic review aimed to evaluate the association between seminal microbiota dysbiosis, inflammatory cytokines, and male infertility, and to explore the potential biological pathways involved in these interactions. **Methods:** This systematic review was synthesized in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Electronic searches of PubMed, Scopus, and Google Scholar were performed to identify studies investigating seminal microbiota, inflammatory cytokines, and male infertility. After screening for eligibility, twelve original English-language articles published between 2014 and 2025 were included in this review. References published outside the predefined review period (January 2014–March 2025), as well as review articles published within this period, were cited in the manuscript and associated tables solely to provide supplementary background context and were excluded from the systematic review findings. Data on microbial pathogens, cytokine profiles, semen parameters, and fertility outcomes were extracted and synthesized qualitatively. In addition, *in silico* pathway enrichment analyses were performed using STRING, Gene Ontology, KEGG, Reactome, and Wiki Pathways databases. **Results:** The included studies consistently demonstrated associations between genital tract infections and elevated levels of inflammatory mediators, including Interleukins (IL) such as IL-1β, IL-6, IL-8, TNF-α, IL-17, IL-18, and Interferon-gamma (IFN-γ). Commonly reported pathogens included *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Mycoplasma genitalium*, *Helicobacter pylori*, and other bacterial species associated with bacteriospermia and prostatitis. Increased cytokine concentrations were frequently associated with impaired sperm motility, abnormal morphology, reduced viability, oxidative stress, DNA damage, and altered semen quality. Pathway enrichment analyses suggested potential involvement of immune and inflammatory signaling pathways, including Janus Kinase-Signal Transducer and Activator of Transcription pathway (JAK–STAT), Toll-like receptor (TLR), Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB), and Nucleotide-binding Oligomerization Domain (NOD-like receptor). However, these findings were derived from bioinformatic analyses and should be considered hypothesis-generating because direct pathway activation was not evaluated in the included studies. **Conclusion:** Current evidence suggests that seminal microbiota dysbiosis may contribute to male infertility through inflammatory and immune-mediated mechanisms involving elevated pro-inflammatory cytokines and impaired sperm function. This systematic review underscores the potential link between the upregulation of pro-inflammatory cytokines and male infertility, suggesting that restoring microbiome balance and modulating the immune response could serve as promising therapeutic strategies to improve male infertility outcomes. https://www.crd.york.ac.uk/PROSPERO/view/CRD420251103886, identifier: CRD420251103886.

Keywords: male infertility; semen; microbiota; dysbiosis; cytokines; inflammation; sperm motility; genital diseases, male

Copyright: © 2026 The Author(s). Published by IMR Press.
This is an open access article under the CC BY 4.0 license.

Publisher's Note: IMR Press stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

Infertility is a complex disorder characterized by the inability to conceive following one year of unprotected intercourse. It affects millions of couples worldwide with multiple underlying causes [1,2]. It is estimated that 40% of infertility cases are attributable to male factors, 40% to female factors, 10% to combined causes, and 10% remain unexplained [3,4]. Among the male-specific causes, factors such as genetic mutations, lifestyle-related stressors, exposure to endocrine disruptors, medical conditions, infections, and certain medications can impair sperm count, motility, and morphology [5]. Notably, infections of the male genital-urinary tract account for approximately 6–10% of male infertility cases [6]. These infections, caused by bacteria, fungi, viruses, and protozoa, may be transmitted through sexual contact, retrograde urinary spread, or hematogenous routes [7,8].

While the human body hosts trillions of microorganisms across various systems, the reproductive tract microbiota has only recently gained attention. In females, *Lactobacillus species* dominate and play protective roles in maintaining vaginal pH, preventing infections, and supporting fertility [9]. In contrast, the male reproductive tract microbiome, particularly in the urethra and coronal sulcus, is less studied but includes lactic acid bacteria (*Lactobacilli*, *Streptococci*), skin flora (*Corynebacteria*, *Staphylococci*), and anaerobes [10,11,12]. The seminal microbiota is composed of commensal bacteria, such as *Lactobacillus and Bifidobacterium* species, which have been associated with better semen parameters and anti-inflammatory effects [1,13,14]. These microbial communities are influenced by internal factors like hormonal balance and circadian rhythms, as well as external factors such as diet and lifestyle, and disturbances in these can lead to dysbiosis [11,13]. Emerging evidence suggests that such dysbiosis may negatively impact male reproductive health by impairing sperm motility, DNA integrity, and mitochondrial function, while also contributing to conditions like preterm birth and neonatal complications [1,11,15]. A potential mechanism linking Gram-negative bacteria to male infertility involves lipopolysaccharide (LPS), a component of their outer membrane. Elevated levels of Gram-negative bacteria, including *E. coli*, are found in the semen of men with asthenospermia and oligoasthenospermia [12]. LPS activates Toll-like receptor 4 (TLR4), initiating immune responses that can cause sperm DNA fragmentation and reduce fertilization capacity [16]. Additionally, bacterial virulence factors, such as hemolysins, fimbriae, and the sperm immobilization factor (SIF), disrupt sperm membranes and impair motility [17]. An abundance of *Lactobacillus* in some infertile men has been observed to acidify semen and disrupt sperm function [12]. Moreover, reduced microbial diversity in azoospermic patients is linked to altered metabolic and immune gene expression, affecting spermatogenesis and lipid metabolism [12,18]. Female reproductive conditions, such as bacterial vaginosis, can also indirectly impact sperm by increasing ROS production, thereby impairing sperm function [19].

Given the growing recognition of the seminal microbiome's role in fertility, it is imperative to identify microbial biomarkers and their interaction with the host immune system. In the present study, we collected existing data on the composition of bacterial communities [20] and used *in silico* tools to analyze the interaction of different bacteria in general and pathogenic taxa in particular with the male reproductive tract, which may elevate pro-inflammatory cytokine responses. Such insights provide a framework for understanding how disturbances in microbial ecosystems could lead to poor-quality sperm production and male infertility. We explore their involvement in immune signalling pathways, biological functions, and molecular mechanisms contributing to infertility, thereby offering insights into potential diagnostic and therapeutic targets.

2. Materials and Methods

This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) at the National Institute for Health Research (PROSPERO ID: CRD420251103886) and was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (**PRISMA**) [21] guidelines to investigate the association between dysbiosis of seminal plasma microbiota and the expression of pro-inflammatory cytokines in adult males. The research question was formulated using the **PICO** (Population, Intervention, Comparison, Outcome) framework [22], including the inclusion and exclusion criteria. The components of the PICO strategy were defined as follows:

- **Population (P)**: Adult maleindividuals
- **Intervention (I)**: Presence and characterization of seminal microbiota and associated pro-inflammatory cytokines.
- **Comparison (C)**: Comparisons between fertile and infertile men.
- **Outcome (O)**: Semen quality indicators, including sperm count, motility, morphology, and other parameters related to male reproductive health.

2.1 Search Strategy

A thorough literature search was performed in three primary databases- PubMed, Scopus, and Google Scholar to retrieve studies published from January 2014 to March 2025 that examined the relationship between seminal microbiota dysbiosis and pro-inflammatory cytokines release in infertile men. The search strategy was formulated by integrating methodologies from two prior systematic reviews on male infertility [23,24] and focused on three key domains: male infertility, seminal microbiota, and pro-inflammatory cytokines.

For the male infertility component, search terms included: "semen", "sperm", "spermatozoa", "oligozoospermia", "asthenozoospermia", "teratozoospermia", "male subfertility", "male infertility", "spermatogenesis", "infertile male", and "infertile men". PubMed searches were enhanced using the MeSH term "Male Infertility" with Boolean "OR".

Search terms for seminal microbiota focused on bacterial species such as "*E. coli*", "*Staphylococcus*", "*Neisseria*", "*Ureaplasma*", "*Gonorrhoea*", "*Chlamydia*", and "*Treponema*". For pro-inflammatory cytokines, keywords included "Tumor Necrosis Factor- alpha(TNF-α)", "IL-6", "IL-1β", "IL-17", "IFN-γ", "IL-18", "Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)", "IL-8", "IL-2", "IL-23", and "IL-12".

These three groups were combined using the Boolean operator "AND" (e.g., [male infertility] AND [bacterial genus] AND [Pro-inflammatory cytokine]). Multiple keyword combinations were employed to enhance retrieval sensitivity. Search results were exported into reference management software, and duplicate removal was performed by Zotero to retain unique study records. (Zotero Citation Manager software, https://www.zotero.org/).

2.2 Inclusion and Exclusion Criteria

The screening process was guided by specific inclusion and exclusion criteria, with eligibility restricted to original full-text, English-language publications between January 2014 and March 2025, related to human male participants. Studies on female subjects or animals, review articles, book chapters, conference abstracts, editorials, and case studies were excluded. References published outside the predefined review period (January 2014–March 2025), as well as review articles published within this period, were cited in the manuscript and associated tables solely to provide supplementary background context and were excluded from the systematic review findings.

All inclusion and exclusion criteria are summarized in **Supplementary Table 1**. Eligibility assessment was performed through the manual screening of titles and abstracts, following the established criteria. This initial screening was conducted using information from the title, keywords, and abstract. Articles that met the preliminary criteria proceeded to the full-text review stage, during which the complete articles were assessed in detail to confirm their relevance and adherence to inclusion standards. The final pool of studies was identified after full-text review at the eligibility stage, ensuring alignment with the specified inclusion and exclusion parameters. Discrepancies in selection, if any, were resolved through discussion among the authors. As this is a systematic review of published literature, ethics approval was not required.

2.3 Quality Assessment

The included studies were subjected to quality assessment using the Newcastle-Ottawa Scale (NOS) [25], which assesses non-randomized studies based on three broad domains: Selection, Comparability, and Outcome. In the Selection domain, studies were evaluated based on the representativeness of the exposed cohort, the suitability of the selection of the controls, ascertainment of exposure, and confirmation that the outcome of interest was not present at the start of the study. In the comparability domain, points were allocated for managing significant confounders, notably age, coexisting infection, along with additional characteristics such as lifestyle, abstinence period, varicocele, and hormonal status. The Outcome domain focuses on the method of outcome assessment, the standardization and reproducibility of measurements, and the completeness of results. Studies that attained a score of 8 or more stars (out of 9) were categorized as low risk of bias, those scoring 6 and 7 stars were classified as having a moderate risk of bias, whilst studies obtaining 5 and less than 5 stars were considered high risk of bias. Each study was independently evaluated by two reviewers, and discrepancies were resolved by consensus.

This systematic review included predominantly cross-sectional studies. Of the 12 studies included in this review, 10 were observational studies, predominately cross-sectional in design, and were therefore eligible for NOS assessment. Two studies [26,27] employed laboratory-based experimental designs and were therefore not suitable for NOS assessment, as the tool is intended for observational research. These studies were instead subjected to a qualitative methodological assessment focusing on experimental design, outcome measurement, and relevance to the review objective.

Quality assessment was performed independently using predefined criteria, and any discrepancies were resolved through discussion. The results of the quality assessment are presented in **Supplementary Table 2**. The findings of the risk of bias evaluation were considered during data synthesis and interpretation of the evidence.

2.4 In Silico Protein-Protein Interaction Analysis

2.4.1 Data Categorization and Analysis

The information collected from the literature search was further categorized into the presence/absence and the impact of various seminal bacterial species on the expression levels of pro-inflammatory cytokines in infertile and fertile men. This categorization was designed to identify patterns linking microbial dysbiosis to alterations in the immune response and subsequent sperm dysfunction.

2.4.2 *In Silico* Functional and Pathway Analysis

To further elucidate the underlying molecular mechanisms by which pro-inflammatory cytokines influence sperm parameters and contribute to male infertility, *in sil-*

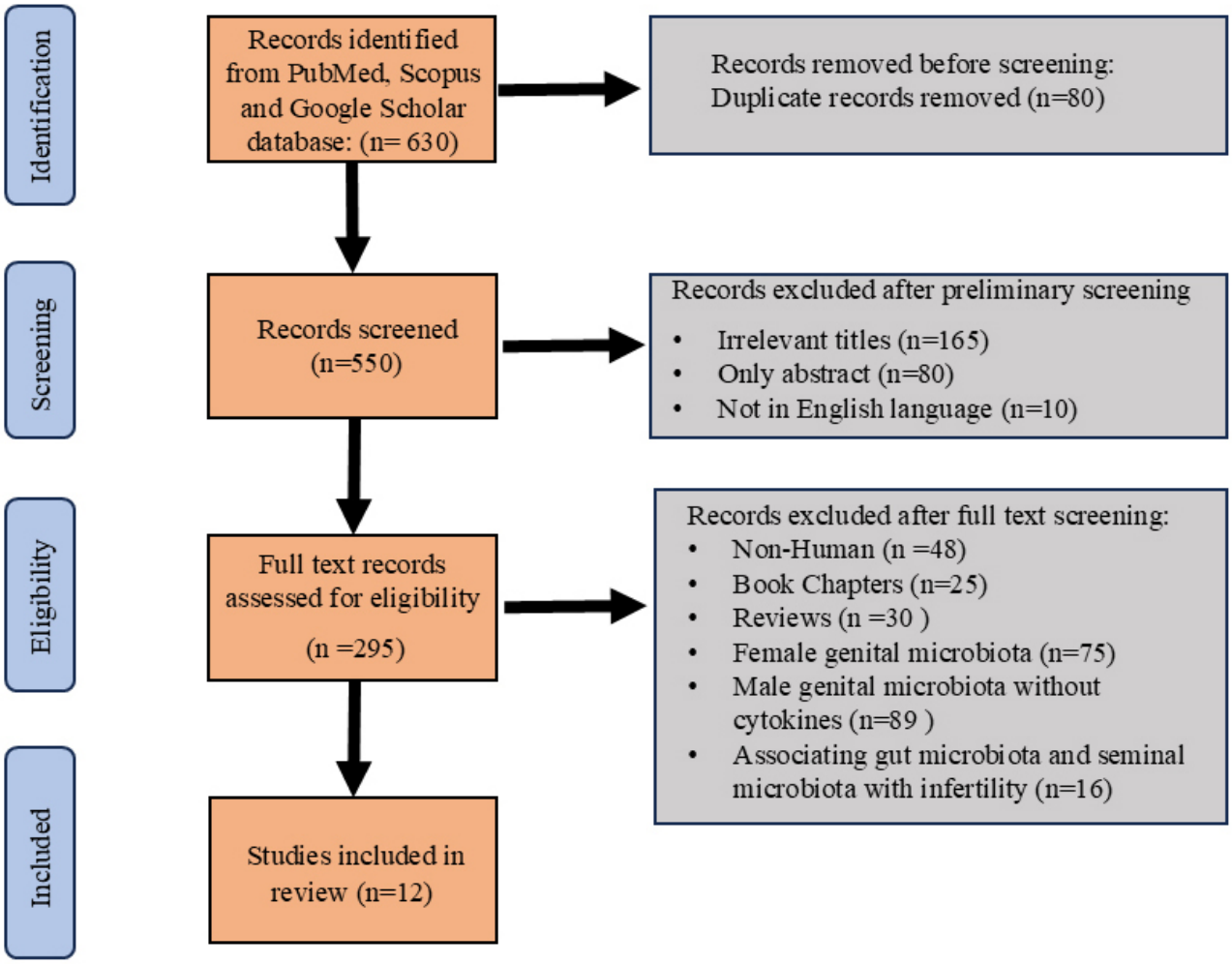


Fig. 1. PRISMA flow diagram showing the number of records identified through database searching, the number after duplicate removal, the number screened by title/abstract, records, excluded, full-text articles assessed for eligibility, and studies in the final review. PRISMA flow diagram showing the number of records identified through database searching, the number after duplicate removal, the number screened by title/abstract, records excluded, full-text articles assessed for eligibility, and studies included in the final review.

ico analyses were conducted. The STRING v11.5 database (https://string-db.org/) was utilized to construct protein-protein interaction (PPI) networks of the identified cytokines. This analysis identified core hub proteins and interacting networks that may contribute to male infertility and reproductive dysfunction.

2.4.3 Gene Ontology and Pathway Enrichment

Functional enrichment analyses were performed using Gene Ontology (GO) to identify the biological processes, cellular components, and molecular functions associated with these cytokines. In addition, pathway enrichment analyses were performed using the KEGG, Reactome, and WikiPathways databases to identify key signalling pathways relevant to inflammation, immune regulation, oxidative stress, and apoptosis in the context of male infertility.

3. Results

3.1 Study Selection

As illustrated in the PRISMA flow diagram (Fig. 1), the preliminary search across PubMed, Scopus, and Google Scholar combined a total of 630 records. Following the removal of 80 duplicate articles, 550 records remained for screening. Titles and abstracts of the remaining articles were thoroughly reviewed. After the eligibility assessment of full-text articles, a total of 12 original research articles were included in this systematic review. Based on predefined inclusion and exclusion criteria, the following exclusions were made:

- **Irrelevant studies** (e.g., those focusing on gut microbiota, Coronavirus Disease 2019 (COVID-19), unrelated diseases): *n = 165*.
- **Animal studies**: *n = 48*.
- **Studies on female genital microbiomes**: *n = 75*.



Fig. 2. Risk of bias assessment of included studies using the Newcastle-Ottawa Scale. The figure present domain-level methodological quality assessments and the total NOS score for each included observational study (maximum score: 9 points). Studies scoring 8–9 were classified as low risk, those scoring 6–7 as moderate risk, and those scoring less than equal to 5 as high risk according to the predefined criteria used in the review. Green and red circles indicate positive and negative domain level judgements respectively. The total NOS score and corresponding overall category are provided for each study.

• **Review articles**: *n = 30*.

• **Only abstract, book chapters, case reports**: *n = 105*.

Among the 10 observational studies assessed using the NOS, four were classified as having a low risk of bias, five as having a moderate risk of bias, and one as having a high risk of bias (Fig. 2). The methodological quality of the included observational studies was evaluated using a modified Newcastle–Ottawa Scale (NOS) adapted for cross-sectional and case-control studies. Of the 12 studies included in the systematic review, 10 observational studies were eligible for NOS assessment, comprising seven

Table 1. Region-specific bacterial communities (commensal and pathogenic) in the male reproductive tract.

Regions of the male reproductive tract	Harbored bacteria	Effects	References
Testis	Actinobacteria	Common commensal phylum in normal testis, dominant in iNOA patients with no sperm retrieval, and negatively associated with testicular sperm quality	[28,29]
	Firmicutes, Bacteroidetes	Common commensal, negatively associated with sperm quality in both semen and testis, dominates in iNOA cases	[18]
	Proteobacteria	Common in healthy testis, decreased in iNOA, positively associated with sperm quality.	[29]
	Escherichia coli	Pathogenic, causes orchitis and epididymitis, associated with testicular inflammation	[30]
	Klebsiella Spp.	Pathogenic, linked with testicular inflammation, orchitis, and epididymitis	[31]
Epididymis	*Neisseria gonorrhoeae*	The most common cause of epididymitis in young, sexually active males	[32]
	Chlamydia trachomatis	The most common cause of epididymitis in young, sexually active males	[32]
	Pseudomonas aeruginosa	Cause epididymitis and orchitis contribute to chronic infections	[33]
Vas Deferens	*Chlamydia trachomatis, Escherichia coli, Mycobacterium tuberculosis*	Acute Vasitis	[34]
Urethra	*Corynebacterium* species	Commensal bacteria maintain microbial balance	[35]
	Corynebacterium glucuronolyticum	Pathogenic bacteria Responsible for Urethritis and involved in showing the symptoms	[36]
	Staphylococcus species	Causes urinary tract infection	[37]
Glans penis	*Staphylococcus warneri*	Balanoposthitis	[38]
	Prevotella bivia	Balanoposthitis and male genital lichen sclerosus	[39]
	Enterobacteriaceae		
	Fusobacterium		
	Anaerococcus	Present predominantly in uncircumcised men, contributes to an anaerobic environment	[40]

iNOA, idiopathic non-obstructive azoospermia.

Table 2. Bacterial genera implicated in male infertility disorders.

Disease	Bacteria involved (Genus)	References
Azoospermia	*Lactobacillus, Enterococcus, Corynebacterium, Veillonella, Gardnerella, Ureaplasma, Prevotella*	[18,41]
Oligozoospermia	*Serratia, Escherichia, Lactobacillus, Shuttleworthia, Prevotella*	[12,41]
Asthenozoospermia	*Sneathia, Ralstonia, Ureaplasma, Bacteroides, Chryseobacterium*	[12]
Oligo-asthenozoospermia	*Ralstonia, Oscillospira, Parabacteroides, Lachnospira, Phascolarctobacterium*	[12]
Teratozoospermia	*Streptococcus, Ureaplasma*	[42,43]
Oligoasthenoteratozoospermia	*Pseudomonas, Klebsiella, Aerococcus, Actinobaculum, Neisseria*	[44]

cross-sectional studies and three case-control studies. Two laboratory-based experimental studies [26,27] were not assessed using the NOS because the tool does not apply to experimental study designs.

3.2 Region-Specific Bacterial Communities and Male Infertility

The male genital system, which includes the testes, epididymis, prostate, seminal vesicles, and urethra, is home to diverse bacterial communities. These microbial communities include both commensals and harmful microbes. Commensal bacteria contribute to immune homeostasis and epithelial integrity, whereas pathogenic bacteria induce local inflammation and oxidative stress, thereby impairing sperm function. Dysbiosis, or bacterial imbalance, has increasingly been implicated in male infertility through mechanisms of change in sperm motility, DNA breakage, and abnormal semen parameters. The presence of certain bacteria, including *Ureaplasma*, *Mycoplasma*, and *Escherichia coli*, has been associated with compromised sperm quality and inflammation. Microbial metabolites and toxins further damage the testicular and epididymal environments. Table 1 (Ref. [18,28,29,30,31,32,33,34,35,36,37,38,39,40]) and Table 2 (Ref. [12,18,41,42,43,44]) provide an overview of the major bacterial taxa identified in different regions of the male reproductive tract and their possible correlations with male infertility.

3.3 Commensal to Pathogen Transition of Bacteria in Male Infertility

Several commensal bacteria in the male reproductive tract help maintain mucosal homeostasis, modulate the immune system, and provide resistance to pathogen invasion. In optimal settings, these bacteria exist in harmony with the host, frequently without eliciting clinical manifestations. Nevertheless, specific situations can instigate a commensal-to-pathogen shift, transforming these bacteria into opportunistic agents of infection and inflammation that impair male reproductive health [15]. Among them, *Lactobacillus* species are the most widely studied, as they contribute to maintaining seminal plasma balance by producing lactic acid, hydrogen peroxide, and bacteriocins that inhibit pathogen overgrowth [45]. However, in conditions of dysbiosis, immune suppression, or excessive colonization, certain strains of *Lactobacillus*, like *Lactobacillus iners* and *L. gasseri*, may disturb the seminal pH by excessive production of lactic acid, negatively affecting sperm motility and viability, and contributing to oxidative stress [15,46,47]. Similarly, *Corynebacterium* species, which are part of the normal urethral and seminal microbiota, are usually non-pathogenic but can shift toward opportunism under altered host defenses, occasionally causing urethritis, prostatitis, or sperm membrane damage [35,39]. As per a report, *Lactobacillus iners* stimulates the overproduction of *Corynebacterium* spp, which leads to a reduction in metabolites conducive to spermatogenesis [48]. *Staphylococcus epidermidis*, a commensal organism of the skin and mucosa, is generally non-pathogenic; yet, under some circumstances, it can stick to the surface receptors on spermatozoa, resulting in irreversible sperm agglutination that diminishes motility and promotes oxidative stress. These bacterial species affect the motility and morphology of the sperm by changing the pH and viscosity of the semen [49]. Thus, while these bacteria function as part of the normal protective flora of the male reproductive system, factors such as antibiotic exposure, biofilm development, and altered microbial diversity can drive their transition into opportunistic pathogens, ultimately contributing to impaired semen quality and male infertility.

3.4 Association of Pro-Inflammatory Cytokines and Male Infertility

Cytokines are critical chemical messengers that are crucial for immunological responses and inflammation in the male reproductive tract. Physiologically, they assist in spermatogenesis and testicular immune privilege. Pathologically, the overexpression of pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β, and IFN-γ may disrupt testicular homeostasis and hinder spermatogenesis [50]. These cytokines are known to produce oxidative stress, disrupt the blood-testis barrier, and induce germ cell apoptosis, resulting in diminished sperm count, motility, and viability [51]. Inflammation in the male reproductive tract has also been implicated in compromised semen quality and infertility. Major inflammatory cytokines implicated in male infertility and their reported impact on reproductive function are highlighted in Table 3 (Ref. [27,51,52,53,54,55,56,57,58,59,60,61,62,63]).

3.5 In Silico Analysis

Protein-protein interaction analysis (**Supplementary Fig. 1**) of pro-inflammatory cytokines using the STRING network suggested their involvement in key biological processes (**Supplementary Table 3**), including cellular response to lipopolysaccharide (GO:0071222; false discovery rate $p = 6.93 \times 10^{-8}$), defense response to Gram-positive bacterium (GO:0050830; FDR $p = 6.19 \times 10^{-7}$), extrinsic apoptotic signaling pathway (GO:0097191; FDR $p = 2.36 \times 10^{-5}$), and inflammatory response (GO:0006954; FDR $p = 8.03 \times 10^{-9}$).

The top pathways identified from KEGG analysis (Table 4) included Toll-like receptor signaling (hsa04620; FDR $p = 1.94 \times 10^{-6}$), JAK-STAT signaling (hsa04630; FDR $p = 1.57 \times 10^{-7}$), and NOD-like receptor signaling (hsa04621; FDR $p = 2.32 \times 10^{-7}$), highlighting potential molecular mechanisms associated with male infertility. Additionally, Reactome pathway analysis indicated that these pro-inflammatory cytokines may exert their effects through pathways such as Signaling by Interleukins (HSA-449147; FDR $p = 1.06 \times 10^{-13}$) and MAPK1/MAPK3 signaling (HSA-5684996; FDR $p = 0.0480$). The wiki pathway analysis showed significant enrichment in immune-related processes. The "Cytokines and inflammatory response" pathway (WP5095) showed a strong association ($p = 4.55 \times 10^{-13}$), followed by "Th17 cell differentiation pathway"

Table 3. Association of pro-inflammatory cytokines in male infertility disorders.

Cytokines	Effects on semen parameters and male reproductive pathways	Molecular mechanisms involved	Bacteria associated	References
TNF-α	↓ sperm quality ↑ ROS sperm chromatin disintegration, acrosome deterioration, DNA fragmentation	Infection promote inflammation and oxidative stress leading to increased phosphatidylserine exposure, reduced mitochondrial membrane potential and sperm DNA fragmentation contributing to male infertility.	*Staphylococcus aureus, E. coli, E. faecalis, Helicobacter pylori*	[52,53]
IL-6	↑ sperm necrosis ↑ seminal pH ↓ sperm quality ↓ sperm motility	Infection causes inflammation and release of pro-inflammatory cytokines, leading to damage of BTB and Sertoli cell tight junctions. Cytokines spill over into the semen and damage spermatozoa. Oxidative stress and lipid peroxidation caused by IL-6 contribute to male infertility, marked by detection of MDA.	*Helicobacter pylori, Staphylococcus aureus, E. coli, Mycoplasma genitalium*	[54,55,56,57]
IL-1β	↓ sperm count ↓ sperm motility ↑ ROS ↑ sperm DNA fragmentation	Activation of molecular chain of events by IL-1β leads to disintegration of the sperm DNA molecule along with apoptosis.	*Chlamydia trachomatis, Staphylococcus aureus, E. coli*	[53,57]
IL-17	Affect spermatogenesis, Inflammation of testis, Increase blood- testis-barrier permeability, Testicular interstitium prostatitis	During infection by pathogens, TH-17 cells contribute to immune response by secreting IL-17. Persistent infection may lead to chronic inflammation, prostate tissue damage, and scarring leading to male infertility.	*Staphylococcus aureus, E. coli*	[58]
IFN-γ	Negative correlation with spermiogram parameters ↓ sperm count, motility, and morphology, Prostatitis	Infection causes tissue lesions that stimulate IL-1, which in turn activates Polymorphonuclear leukocytes (PMN) & macrophages to produce IFN-gamma	*Chlamydia trachomatis gonorrhea*	[57,58,62]
IL-18	↓ sperm quality, lower sperm density, pH, sperm movement, sperm activation rate, survival rate, sperm morphology Sperm apoptosis	Infection cause a significant increase in NO concentration in semen, which activate other reactive oxygen species and affects male reproductive capacity	*Ureaplasma urealyticum Chlamydia trachomatis*	[59,61]
GM-CSF	Infection of prostate epithelial cells	Found in an infertile man's semen sample, role not reported	*Chlamydia trachomatis*	[27,60,63]
IL-8	Prostatitis, loss of sperm function, induce immunological response, chronic inflammation, damage to spermatozoa, increase seminal pH	Infection causes tissue lesions that stimulate IL-1, which in turn activates polymorphonuclear leukocyte (PMN) & macrophages to produce IL-8	*Chlamydia trachomatis, Neisseria gonorrhoeae*	[51,54]
IL-2	Decrease sperm quality, motility, membrane integrity, and mitochondrial activity	Bacterial overload released pro-inflammatory cytokines and free-radicals to cause oxidative damage by lipid peroxidation of sperm membrane	*Staphylococcus aureus, E. coli Enterococcus faecalis*	[53]

Table 3. Continued.

Cytokines	Effects on semen parameters and male reproductive pathways	Molecular mechanisms involved	Bacteria associated	References
IL-23	↑ Chronic Inflammation in male genital tract Prostatitis infection Affect the immunosuppresive microenvironment of testis	Microbiota act as PAMP and stimulate TLR4 to activate testicular T_H17 Cells which leads to inflammation and IL-23 production	*Staphylococcus aureus,* *E. coli* *Klebsiella pneumoniae*	[58]

UP arrow indicate Increase and DOWN arrow indicate Decrease in the respective parameters.

Table 4. Pathway enrichment analysis of pro-inflammatory cytokines present in seminal fluid.

Pathway	Description	Count in the network	Strength	Signal	False discovery rate
KEGG PATHWAYS					
hsa04630	JAK-STAT signalling pathway	5 of 158	1.79	2.84	1.57×10^{-7}
hsa04621	NOD-like receptor signalling pathway	5 of 173	1.76	2.72	2.32×10^{-7}
hsa04620	Toll-like receptor signalling pathway	4 of 100	1.9	2.63	1.94×10^{-6}
hsa05130	Pathogenic Escherichia coli infection	5 of 187	1.72	2.62	3.23×10^{-7}
hsa04064	NF-kappa B signalling pathway	3 of 101	1.77	1.8	0.00015
hsa04658	Th1 and Th2 cell differentiation	2 of 85	1.67	1.12	0.0054
hsa04659	Th17 cell differentiation	6 of 99	2.08	4.36	2.03×10^{-10}
REACTOME PATHWAYS					
HSA-449147	Signalling by Interleukins	10 of 453	1.64	3.68	1.06×10^{-13}
HSA-5684996	MAPK1/MAPK3 Signalling	3 of 283	1.32	0.62	0.0480
WIKI PATHWAYS					
WP5095	Cytokines and inflammatory response	6 of 26	2.66	6.5	4.55×10^{-13}
WP5130	Th17 cell differentiation pathway	6 of 69	2.23	4.93	4.46×10^{-11}
WP4493	Cells and molecules involved in the local acute inflammatory response	3 of 17	2.5	2.86	3.95×10^{-6}
WP75	Toll-like receptor signalling pathway	4 of 102	1.89	2.51	3.95×10^{-6}
WP453	Inflammatory response pathway	2 of 30	2.12	1.54	0.0013
WP1433	Nucleotide-binding oligomerization domain (NOD) pathway	2 of 41	1.98	1.4	0.0022

(WP5130) with $p = 4.46 \times 10^{-11}$, indicating potential involvement in adaptive immunity. "Cells and molecules in local acute inflammatory response" (WP4493) and "Toll-like receptor signaling" (WP75) were also significantly enriched ($p = 3.95 \times 10^{-6}$), suggesting innate immune activation. The "Inflammatory response pathway" (WP453, $p = 0.0013$) and "NOD pathway" (WP1433, $p = 0.0022$) further support the role of inflammation implicated in male infertility (Table 4).

4. Discussion

The expanding body of literature exploring the relationship between seminal microbiota, proinflammatory cytokines, and male infertility suggests a complex interplay between microbial communities, immune responses, and sperm function. While male infertility has traditionally been attributed to sperm quality parameters alone, recent findings indicate that microbial dysbiosis and associated inflammatory responses play a pivotal role in fertility outcomes [46]. This review aimed to explore these interrelationships and evaluate their implications for male infertility.

4.1 Microbial Dysbiosis and Male Infertility

Historically, the seminal environment was considered sterile. However, recent advances in microbiome analysis have unveiled a dynamic and diverse microbial ecosystem within semen. Commensal bacteria such as *Lactobacillus* and *Bifidobacterium* help to maintain immune balance, thereby protecting spermatozoa from oxidative stress and immune-mediated damage [14,45,64]. In contrast, microbial dysbiosis, characterized by an overrepresentation of pathogens such as *Ureaplasma* [65,66], *Mycoplasma* [66,67], *Escherichia coli* [68,69], *Chlamydia trachomatis* [70,71], and *Staphylococcus aureus* [53], has been consistently linked to adverse reproductive outcomes. This suggests that an imbalance in microbial populations can initiate inflammatory cascades that impair sperm quality and functionality (Fig. 3). It will not be out of context to men-

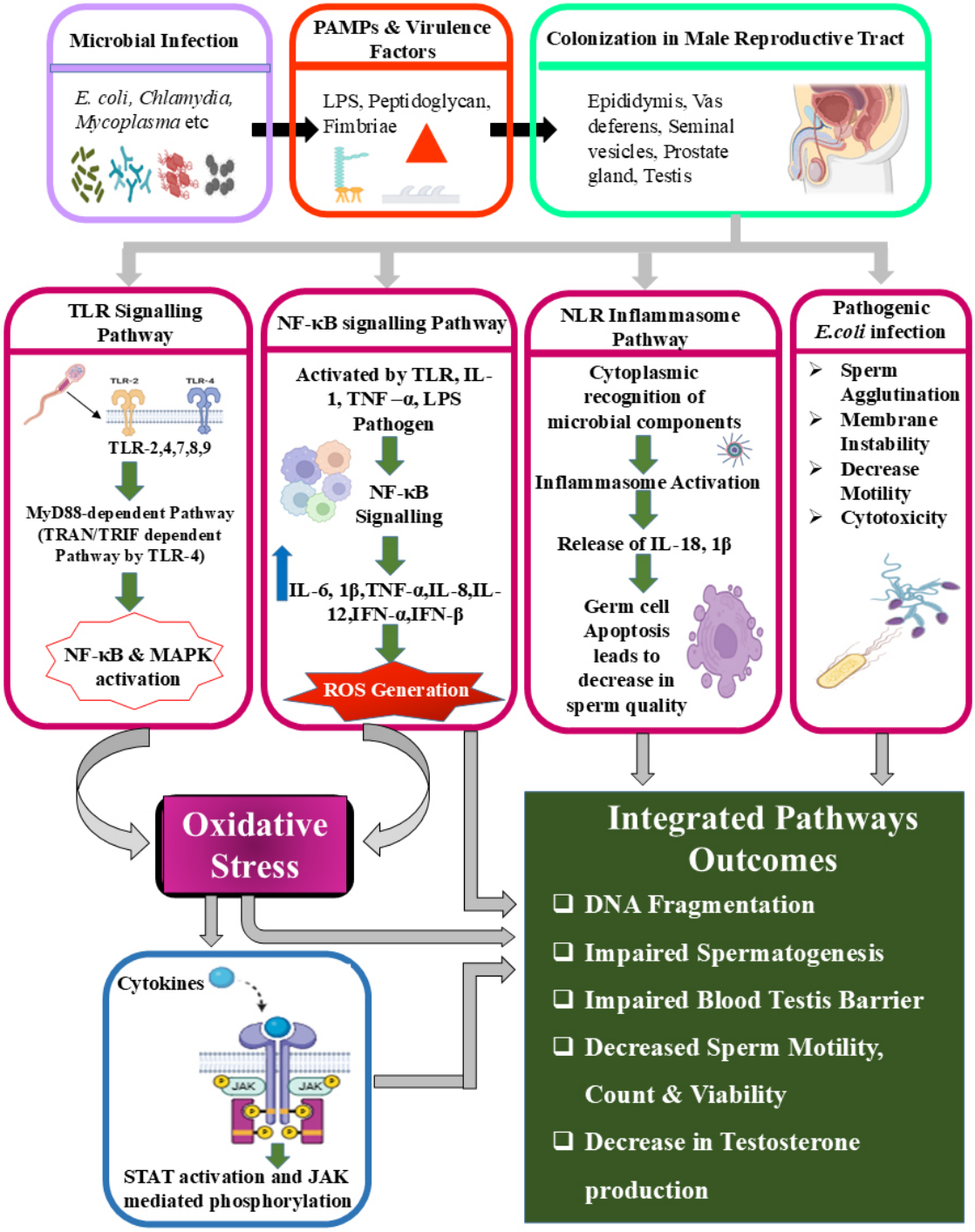


Fig. 3. Proposed inflammatory mechanisms linking male reproductive tract microbial infection to impaired sperm function. The schematic illustrates microbial infection and colonization of the male reproductive tract and the activation of the inflammatory signalling pathways, including Toll-like receptor (TLR), NF-κB, NOD- like receptor (NLR) inflammasome, and JAK/STAT signaling. These responses may promote pro-inflammatory cytokines release and oxidative stress, contributing to sperm DNA fragmentation, impaired spermatogenesis, reduced sperm motility, count, and viability, and altered testosterone production. The figure summarizes the potential mechanisms linking bacterial infection to impaired sperm quality and male reproductive function. Figure created by Biorender.com.

tion here that two recent meta-analyses have independently confirmed detrimental effects of HPV [72] and genital mycoplasma [67] infections on sperm quality and male fertility.

Findings from this review support the hypothesis that seminal microbiota significantly modulate immune responses in the male reproductive tract. Thus, these pathogens may activate the innate immune system, lead-

ing to the release of pro-inflammatory cytokines. These cytokines, in turn, can damage spermatozoa and reduce their fertilizing ability through the activation of various signaling pathways, such as JAK/STAT, TLR, NF-κB, NOD-Like Receptor, and Pathogenic *Escherichia coli* Infection signaling [51,58,71,73,74] (Fig. 4).

4.2 Key Inflammatory Pathways in Male Infertility

4.2.1 JAK/STAT Signaling Pathway (hsa04630)

This pathway plays a crucial role in testicular function, particularly in regulating germline development, stem cell renewal, and sperm capacitation and motility [75]. JAK1 and JAK2 are located in the sperm's equatorial segment and tail, respectively [76]. JAK2, a redox-sensitive kinase, is activated under oxidative stress conditions and is a known contributor to male reproductive problems [77]. Associations between JAK pathway dysregulation and conditions such as oligozoospermia and teratozoospermia have been reported [78,79]. The JAK/STAT pathway is also activated by cytokines like IL-6, TNF-α, and IL-1 [80], whose receptors are expressed in sperm tails [76,81]. So it may be hypothesized that in response to microbial infections in the male reproductive tract, leukocytes release pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1 that activate JAK/STAT signaling [76], reducing sperm motility and count [82,83].

4.2.2 Toll-Like Receptor (TLR) Signaling Pathway (hsa04620)

Toll-like receptors (TLRs) are key components of the innate immune system expressed across multiple cell types, including those in the reproductive system. While their roles in female reproductive tissues such as the ovaries and uterus, particularly in fertilization and implantation, are well established, their expression and functional significance in male germ cells, especially sperm, remain relatively underexplored. In human sperm, TLR2 is localized to the acrosome, midpiece, and principal piece of the tail, whereas TLR4 is distributed across the acrosome, midpiece, and entire tail. These receptors recognize pathogen-associated molecular patterns (PAMPs), including lipopolysaccharide (LPS) and peptidoglycan [84], and their activation by Gram-positive and Gram-negative bacteria reduces sperm motility and viability, thereby impairing fertilization [85].

In addition to TLR2 and TLR4, TLR7 and TLR8, which are highly expressed in X-chromosome-bearing sperm (X-sperm), have received attention for their role in modulating sperm metabolism and selectively reducing X-sperm motility, allowing X and Y sperm to be separated. More broadly, sperm-borne TLRs function as immune sentinels, detecting bacterial and viral infections and influencing reproductive outcomes, including reduced sperm functionality, miscarriage prevention, maternal protection, and even sex selection [85]. In human sperm, TLR2, TLR4, and TLR9 are localized to the acrosome and tail regions [85], and their activation by pathogens such as *E. coli* and *Chlamydia* induces TNF-α production [86]. TNF-α, through TNFR1 binding, promotes apoptosis and has been shown to decrease sperm motility and viability [82]. Furthermore, pro-inflammatory mediators such as IL-6, IL-12, and reactive oxygen species (ROS) generated during TLR activation contribute to DNA fragmentation, impaired motility, and disruption of the blood–testis barrier [87,88], while chronic activation under conditions such as bacterial dysbiosis may trigger autoimmune responses against sperm [89].

Mechanistically, TLR2 and TLR4 act as principal surface receptors that initiate innate immune signaling via MyD88-dependent pathways, leading to activation of NF-κB and MAPK and subsequent pro-inflammatory cytokine production. Notably, TLR4 also engages a TRAM/TRIF-dependent pathway to induce interferon-β (IFN-β), highlighting its distinct role in antiviral responses. Collectively, these pathways underscore the critical involvement of TLRs in inflammation, immune regulation, and reproductive pathophysiology.

4.2.3 NF-κB Signalling Pathway (hsa04064)

NF-κB is a key mediator of inflammation and cell survival. It is activated upon binding of ligand to receptors, such as LPS, IL-6, and TNF-α [90]. Signals from IL-1 activate the adaptor protein MyD88, which in turn activates the inflammatory transcription factor NF-KB. Members of the transforming growth factor-beta (TGF-β) superfamily, such as activins and TGF-βs, signal through serine/threonine kinase receptor subunits to activate SMAD transcription factors [91]. TLR3 and TLR4 are prominently expressed in Leydig cells and facilitate the activation of the NF-κB pathway, subsequently leading to the synthesis of proinflammatory cytokines, such as IL-6 and TNF-α, along with IFN-α and IFN-β [87]. Pathogens such as *Mycoplasma*, *C. trachomatis*, and *E. coli* activate NF-κB, resulting in increased production of IL-6, IL-1β, TNF-α, and ROS, causing oxidative damage to sperm membranes, DNA, and motility [33,92]. Thus, it is hypothesized that bacterial colonization of the male reproductive tract causes infertility by triggering the release of pro-inflammatory cytokines via the NF-KB pathway.

4.2.4 Pathogenic Escherichia coli Infection (hsa05130)

Uropathogenic *E. coli* (UPEC) expresses virulence factors like hemolysins, LPS, and fimbriae that facilitate adherence to sperm and epithelial cells [93,94]. These allow the bacteria to adhere to sperm and epithelial cells, elude the host's defenses, and survive in the genitourinary tract throughout their life cycle. Spermatozoa and E. Coli interact physically, resulting in agglutination, decreased motility, membrane instability, and occasionally direct sperm cytotoxicity [95]. Specifically, the most significant influence

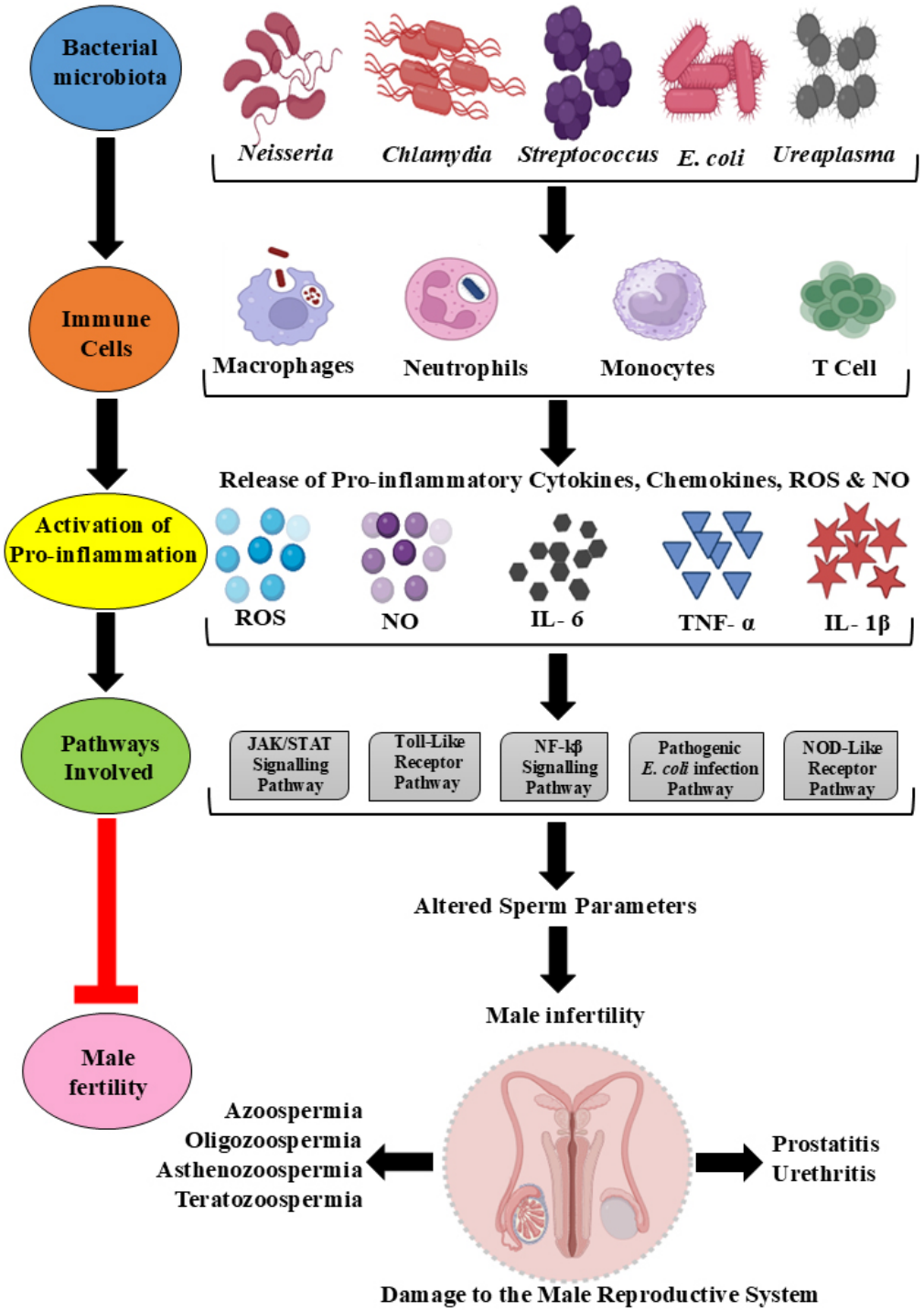


Fig. 4. Proposed mechanisms of bacterial semen infection impairing male fertility. Pathogenic bacteria such as *Neisseria*, *Chlamydia*, *Streptococcus*, *E. coli*, and *Ureaplasma* activate immune cells, including macrophages, neutrophils, monocytes, and T cells. This immune response triggers the release of pro-inflammatory cytokines (IL-6, TNF-α, IL-1β), reactive oxygen species (ROS), and nitric oxide (NO), which may alter signaling pathways, including JAK/STAT, TLR, NF-κB, and NOD-Like Receptor. These signalling alterations may, in turn, adversely affect semen parameters and contribute to male infertility. Figure created by Biorender.com.

of an *E. coli* infection on male infertility, aside from these direct consequences, comes from the host immunological response, the generation of inflammatory cytokines. Nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPKs) are activated when immune cells and testicular somatic cells recognize bacterial components by pattern recognition receptors (PRRs), such as Toll-like receptor 4 (TLR 4) [85,92], triggering cytokine release (TNF-

α, IL-1β, IL-6, IL-8), which negatively affects spermatogenesis and testosterone production [50,96,97].

4.2.5 NOD-Like Receptor (NLR) Signaling Pathway (hsa04621)

NLRs are cytoplasmic receptors that recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), and are vital regulators of inflammation, apoptosis, and early development. Their activation leads to the production of IL-1β and IL-18, contributing to germ cell apoptosis and impaired reproductive function [98,99]. Pathogens like *U. urealyticum* and *N. gonorrhoeae* can stimulate these responses, resulting in elevated levels of IL-1, IL-8, and IL-16 [50]. These cytokines have been linked to DNA damage [100,101], reduced sperm count, motility, and viability [100]. Therefore, it is postulated that the release of these cytokines during bacterial infection may be linked to male infertility through their impact on testicular function and sperm quality via activation of NLR.

5. Research Gap and Future Direction

Despite increasing recognition of the role of seminal microbiota and inflammatory cytokines in male infertility, several important knowledge gaps remain regarding their complex interactions and their contribution to reproductive dysfunction. Current evidence suggests that microbial dysbiosis and immune activation are associated with impaired semen quality; however, the precise mechanisms linking these processes have not been fully elucidated.

First, there is a limited understanding of how individual bacterial communities or specific microbial signatures influence the local immune environment and alter male fertility status. Although certain pathogens, including *Ureaplasma*, *Mycoplasma*, *Escherichia coli*, and *Chlamydia trachomatis*, have been associated with elevated inflammatory mediators and poor semen parameters, the species-specific and strain-specific effects of these microorganisms on sperm physiology remain largely unexplored.

Second, mechanistic insights into how microbial dysbiosis initiates inflammatory signaling, oxidative stress, apoptosis, and disruption of immune homeostasis within the testicular, epididymal, and accessory gland microenvironments are still incomplete. Most currently available evidence is derived from observational studies, which preclude the establishment of causal relationships. Experimental studies using cellular and animal models are therefore required to validate the proposed mechanisms and clarify the molecular pathways involved.

Third, there is a marked lack of longitudinal studies investigating the temporal relationship between changes in seminal microbiota, fluctuations in cytokine profiles, and alterations in reproductive outcomes. Most published studies are cross-sectional in nature and provide only a snapshot of the microbiota–immune interaction. Prospective cohort studies with repeated measurements are needed to determine whether microbial dysbiosis precedes infertility or occurs as a consequence of impaired reproductive function.

Another important gap is the scarcity of well-designed interventional studies evaluating the therapeutic potential of microbiome-modulating strategies, including probiotics, prebiotics, antibiotics, dietary interventions, and fecal or seminal microbiota transplantation. The effectiveness of these approaches in restoring microbial homeostasis, reducing inflammation, and improving semen quality remains largely unknown.

Furthermore, most studies have relatively small sample sizes and are confined to specific populations, limiting the generalizability of their findings. Variability in participant characteristics, infertility definitions, semen collection procedures, sequencing platforms, bioinformatic pipelines, and cytokine detection methods also contributes to substantial heterogeneity across studies. Greater standardization of methodologies is required to facilitate comparison between studies and enable robust quantitative synthesis.

The integration of microbiome composition, cytokine profiles, metabolomics, proteomics, transcriptomics, and host genetic information using systems biology approaches represents another largely unexplored area. Multi-omics studies have the potential to provide a more comprehensive understanding of host–microbe interactions and may uncover novel biomarkers and molecular networks involved in male infertility. The application of advanced computational approaches, artificial intelligence, and machine learning algorithms may further improve biomarker discovery and predictive modeling of reproductive outcomes.

Future investigations should prioritize integrated multi-omics approaches combined with mechanistic validation using *in vitro* and *in vivo* models to establish causality and identify therapeutic targets. Large-scale multicenter studies involving ethnically diverse populations are also needed to enhance external validity. Such efforts may ultimately facilitate the development of precision medicine strategies, including microbiota-targeted therapies and immune-based biomarkers, thereby improving the diagnosis, prognosis, and treatment of male infertility associated with microbial dysbiosis and inflammation. Finally, restriction to English-language studies may have introduced language bias.

6. Limitation

This review is limited by the heterogeneity of included studies regarding participant characteristics, semen collection protocols, and infertility definitions. Most of the included studies are cross-sectional or case-control in design, and the observational nature of the study does not establish causality between microbial dysbiosis and male infertility. Furthermore, STRING-based pathway analysis provides predictive insights using current protein interaction datasets, which may be incomplete or skewed toward well-

studied genes and pathways. Predicted networks do not always accurately reflect biological interactions in the male reproductive system, and they lack experimental validation. Potential confounding factors such as age, BMI, diet, smoking, alcohol consumption, and comorbidities may also influence the interpretation and generalizability of the findings. Moreover, the review focuses primarily on microbiota composition and predicted pathways without integrating a multi-omics study that could provide deeper mechanistic insights.

7. Conclusion

Collectively, the available evidence suggests that alterations in the seminal microbiota are associated with inflammatory responses that may influence male reproductive function and semen quality. The interplay between microbial dysbiosis and host immune signaling, potentially involving pathways such as JAK/STAT, TLR, NF-κB, pathogenic Escherichia coli infection, and NOD-like receptor signaling, may contribute to oxidative stress, cytokine-mediated damage, and impaired spermatogenesis. However, owing to the limited number of studies and the predominance of cross-sectional and observational designs, these associations should be interpreted with caution, and causal relationships cannot be established. The in-silico analyses presented in this study provide hypothesis-generating insights into possible molecular mechanisms linking microbial dysbiosis, inflammatory cytokines, and male infertility, but they do not constitute direct clinical or experimental evidence. Further well-designed longitudinal, mechanistic, and multi-omics studies are required to validate these predicted interactions and to determine their clinical significance. Nevertheless, the findings of this review provide an updated framework for understanding the microbiota–immune axis in male infertility and may support the future development of diagnostic biomarkers and microbiota-targeted therapeutic strategies for infertility associated with infection and inflammation.

Availability of Data and Materials

The data underlying this article are available at https://dx.doi.org/10.1016/j.urology.2015.02.068; https://dx.doi.org/10.3390/ijms23158678; https://dx.doi.org/10.1111/and.12501; https://dx.doi.org/10.5114/ceji.2021.105247; https://dx.doi.org/10.3390/ijms222413467; https://dx.doi.org/10.22207/JPAM.17.2.12; https://dx.doi.org/10.1063/5.0200466; https://dx.doi.org/10.1111/aji.12500; https://dx.doi.org/10.5812/jjm.11152; https://dx.doi.org/10.3109/19396368.2013.833658; https://dx.doi.org/10.1016/j.ijbiomac.2013.12.005; https://dx.doi.org/10.1007/s11033-024-09676-2. The datasets used for the systematic review and bioinformatics analyses are available from the corresponding authors upon reasonable request.

Author Contributions

Conceptualization: LS, SCS, MKPS, SRJ. Data curation: AP, BS, LPP, AKM, AS, LG, JN. Formal analysis: AP, BS, LPP, AKM, AS, LG, JN. Funding acquisition: LS. Investigation: AP, BS, LPP, AKM, AS, LG, JN, MKPS. Methodology: AP, BS, LPP, AKM, AS, LG, JN, MKPS. Software: AP, BS, LPP, AKM, AS, LG, JN. Supervision: LS, SRJ, SCS. Visualization: AP, BS, LPP, AKM, AS, LG, JN. Writing – original draft: AP, BS, LPP, AKM, AS, LG, JN. Writing – review & editing: AP, BS, LPP, AKM, AS, LG, JN, SRJ, MKPS, SCS, LS. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

The graphical abstract was created using BioRender.com and Microsoft PowerPoint, in accordance with the applicable licensing terms.

Funding

The authors thank the following funding agencies for providing doctoral and postdoctoral research fellowships: AP, Mukhyamantri Research Fellowship (MRFT), Odisha State Higher Education Council (OSHEC) (Ref. No. 23M0091754); AKM, Council of Scientific and Industrial Research (CSIR) (Grant Nos. 16/06/2019(i) EU-V and Sept/06/22(i) EU-V); BS, University Grants Commission (UGC), Government of India (NTA Ref. No. 231610066087); LG, Department of Science and Technology (DST), INSPIRE Programme (Grant No. DST/INSPIRE/03/2019/001812); and SRJ, Indian Council of Medical Research (ICMR) (Grant No. 2021–10784/CMB-BMS). This work was supported by the Higher Education Department, Government of Odisha, India, through financial assistance to the Centre of Excellence for Environment and Public Health, Ravenshaw University, Cuttack (Grant No.: 874-OSHEC-ACAD-SANC-OO1-2025).

Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/FBL52686.

References

[1] Garcia-Segura S, Del Rey J, Closa L, Garcia-Martínez I, Hobeich C, Castel AB, et al. Seminal Microbiota of Idiopathic In-

fertile Patients and Its Relationship With Sperm DNA Integrity. Frontiers in Cell and Developmental Biology. 2022; 10: 937157. https://doi.org/10.3389/fcell.2022.937157
[2] Kaltsas A, Zachariou A, Markou E, Dimitriadis F, Sofikitis N, Pournaras S. Microbial Dysbiosis and Male Infertility: Understanding the Impact and Exploring Therapeutic Interventions. Journal of Personalized Medicine. 2023; 13: 1491. https://doi.org/10.3390/jpm13101491
[3] Agarwal A, Baskaran S, Parekh N, Cho CL, Henkel R, Vij S, et al. Male infertility. Lancet (London, England). 2021; 397: 319–333. https://doi.org/10.1016/S0140-6736(20)32667-2
[4] Kumar N, Singh AK. Trends of male factor infertility, an important cause of infertility: A review of literature. Journal of Human Reproductive Sciences. 2015; 8: 191–196. https://doi.org/10.4103/0974-1208.170370
[5] Fainberg J, Kashanian JA. Recent advances in understanding and managing male infertility. F1000Research. 2019; 8: 670. https://doi.org/10.12688/f1000research.17076.1
[6] Schuppe HC, Pilatz A, Hossain H, Diemer T, Wagenlehner F, Weidner W. Urogenital Infection as a Risk Factor for Male Infertility. Deutsches Arzteblatt International. 2017; 114: 339–346. https://doi.org/10.3238/arztebl.2017.0339
[7] Sykes JE, Westropp JL. Bacterial Infections of the Genitourinary Tract. Canine and Feline Infectious Diseases. 2014: 871–885. https://doi.org/10.1016/B978-1-4377-0795-3.00089-2
[8] Zuber A, Peric A, Pluchino N, Baud D, Stojanov M. Human Male Genital Tract Microbiota. International Journal of Molecular Sciences. 2023; 24: 6939. https://doi.org/10.3390/ijms24086939
[9] Souza SVD, Monteiro PB, Moura GAD, Santos NO, Fontanezi CTB, Gomes IDA, et al. Vaginal microbioma and the presence of Lactobacillus spp. as interferences in female fertility: A review system. JBRA Assisted Reproduction. 2023; 27: 496–506. https://doi.org/10.5935/1518-0557.20230006
[10] Koort K, Sõsa K, Türk S, Lapp E, Talving E, Karits P, et al. Lactobacillus crispatus-dominated vaginal microbiome and Acinetobacter-dominated seminal microbiome support beneficial ART outcome. Acta Obstetricia et Gynecologica Scandinavica. 2023; 102: 921–934. https://doi.org/10.1111/aogs.14598
[11] Venneri MA, Franceschini E, Sciarra F, Rosato E, D'Ettorre G, Lenzi A. Human genital tracts microbiota: dysbiosis crucial for infertility. Journal of Endocrinological Investigation. 2022; 45: 1151–1160. https://doi.org/10.1007/s40618-022-01752-3
[12] Yang H, Zhang J, Xue Z, Zhao C, Lei L, Wen Y, et al. Potential Pathogenic Bacteria in Seminal Microbiota of Patients with Different Types of Dysspermatism. Scientific Reports. 2020; 10: 6876. https://doi.org/10.1038/s41598-020-63787-x
[13] Magill RG, MacDonald SM. Male infertility and the human microbiome. Frontiers in Reproductive Health. 2023; 5: 1166201. https://doi.org/10.3389/frph.2023.1166201
[14] Oliveira LCSDL, Costa EC, Martins FDG, Rocha ASD, Brasil GA. Probiotics supplementation in the treatment of male infertility: A Systematic Review. JBRA Assisted Reproduction. 2024; 28: 341–348. https://doi.org/10.5935/1518-0557.20240013
[15] Osadchiy V, Belarmino A, Kianian R, Sigalos JT, Ancira JS, Kanie T, et al. Semen microbiota are dramatically altered in men with abnormal sperm parameters. Scientific Reports. 2024; 14: 1068. https://doi.org/10.1038/s41598-024-51686-4
[16] Fraczek M, Szumala-Kakol A, Dworacki G, Sanocka D, Kurpisz M. In vitro reconstruction of inflammatory reaction in human semen: effect on sperm DNA fragmentation. Journal of Reproductive Immunology. 2013; 100: 76–85. https://doi.org/10.1016/j.jri.2013.09.005
[17] Tvrdá E, Ďuračka M, Benko F, Lukáč N. Bacteriospermia - A formidable player in male subfertility. Open Life Sciences. 2022; 17: 1001–1029. https://doi.org/10.1515/biol-2022-0097
[18] Chen H, Luo T, Chen T, Wang G. Seminal bacterial composition in patients with obstructive and non-obstructive azoospermia. Experimental and Therapeutic Medicine. 2018; 15: 2884–2890. https://doi.org/10.3892/etm.2018.5778
[19] Damke E, Kurscheidt FA, Irie MMT, Gimenes F, Consolaro MEL. Male Partners of Infertile Couples With Seminal Positivity for Markers of Bacterial Vaginosis Have Impaired Fertility. American Journal of Men's Health. 2018; 12: 2104–2115. https://doi.org/10.1177/1557988318794522
[20] Jendraszak M, Skibińska I, Kotwicka M, Andrusiewicz M. The elusive male microbiome: revealing the link between the genital microbiota and fertility. Critical review and future perspectives. Critical Reviews in Clinical Laboratory Sciences. 2024; 61: 559–587. https://doi.org/10.1080/10408363.2024.2331489
[21] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ (Clinical Research Ed.). 2021; 372: n71. https://doi.org/10.1136/bmj.n71
[22] Kloda LA, Boruff JT, Cavalcante AS. A comparison of patient, intervention, comparison, outcome (PICO) to a new, alternative clinical question framework for search skills, search results, and self-efficacy: a randomized controlled trial. Journal of the Medical Library Association : JMLA. 2020; 108: 185–194. https://doi.org/10.5195/jmla.2020.739
[23] Farahani L, Tharakan T, Yap T, Ramsay JW, Jayasena CN, Minhas S. The semen microbiome and its impact on sperm function and male fertility: A systematic review and meta-analysis. Andrology. 2021; 9: 115–144. https://doi.org/10.1111/andr.12886
[24] Gomes IDA, Monteiro PB, Moura GAD, Santos NO, Fontanezi CTB, Souza SVD, et al. Microbiota and seminal quality: A systematic review. JBRA Assisted Reproduction. 2023; 27: 507–513. https://doi.org/10.5935/1518-0557.20230008
[25] Ottawa Hospital Research Institute. n.d. Available at: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (Accessed: 20 August 2025).
[26] Carrasquel G, Camejo MI, Michelangeli F, Ruiz MC. IFN-gamma alters the human sperm membrane permeability to Ca(2+). Systems Biology in Reproductive Medicine. 2014; 60: 21–27. https://doi.org/10.3109/19396368.2013.833658
[27] Tanhaye Kalate Sabz F, Hosseini E, Amjadi FS, Mohammadian M, Zandieh Z, Mohammadian F, et al. In vitro effect of granulocyte-macrophage colony-stimulating factor (GM-CSF) on the expression of genes related to sperm motility and energy metabolism and intracytoplasmic sperm injection outcomes in obstructive azoospermic patients. Molecular Biology Reports. 2024; 51: 727. https://doi.org/10.1007/s11033-024-09676-2
[28] Alfano M, Ferrarese R, Locatelli I, Ventimiglia E, Ippolito S, Gallina P, et al. Testicular microbiome in azoospermic men-first evidence of the impact of an altered microenvironment. Human Reproduction (Oxford, England). 2018; 33: 1212–1217. https://doi.org/10.1093/humrep/dey116
[29] Brandão P, Gonçalves-Henriques M, Ceschin N. Seminal and testicular microbiome and male fertility: A systematic review. Porto Biomedical Journal. 2021; 6: e151. https://doi.org/10.1097/j.pbj.0000000000000151
[30] Alzaidi JR, Kareem A. The Impact of Urogenital Tract Infectious Bacteria on Male Fertility. Medical Journal of Babylon. 2024; 21: 476–480. https://doi.org/10.4103/MJBL.MJBL_75_24
[31] Santacroce L, Imbimbo C, Ballini A, Crocetto F, Scacco S, Cantore S, et al. Testicular Immunity and Its Connection with the Microbiota. Physiological and Clinical Implications in the Light of Personalized Medicine. Journal of Personalized Medicine. 2022; 12: 1335. https://doi.org/10.3390/jpm12081335
[32] McConaghy JR, Panchal B. Epididymitis: An Overview. American Family Physician. 2016; 94: 723–726.
[33] Wang S, Zhang K, Yao Y, Li J, Deng S. Bacterial Infections Af-

fect Male Fertility: A Focus on the Oxidative Stress-Autophagy Axis. Frontiers in Cell and Developmental Biology. 2021; 9: 727812. https://doi.org/10.3389/fcell.2021.727812
[34] Al-Gburi S, Patel S. A Rare Case of Acute Vasitis. Cureus. 2023; 15: e51337. https://doi.org/10.7759/cureus.51337
[35] Plummer EL, Ratten LK, Vodstrcil LA, Murray GL, Danielewski JA, Fairley CK, et al. The Urethral Microbiota of Men with and without Idiopathic Urethritis. mbio. 2022; 13: e0221322. https://doi.org/10.1128/mbio.02213-22
[36] Meštrović T, Neuberg M, Sviben M, Ribić R, Drenjančević D, Škrlec I, et al. Corynebacterium glucuronolyticum in men with and without urethritis syndrome: An underrecognized pathogen or a bona fide commensal? Infectious Diseases now. 2022; 52: 441–446. https://doi.org/10.1016/j.idnow.2022.08.002
[37] Farrell RM. Exploring the bacterial diversity of the male urethra during idiopathic urethritis [master's thesis]. Indianapolis: Indiana University; 2020. Available at: https://hdl.handle.net/1805/23693 (Accessed: 5 January 2026).
[38] Gonçalves MFM, Fernandes ÂR, Rodrigues AG, Lisboa C. Microbiome in Male Genital Mucosa (Prepuce, Glans, and Coronal Sulcus): A Systematic Review. Microorganisms. 2022; 10: 2312. https://doi.org/10.3390/microorganisms10122312
[39] Ruiz-Pino M, Foronda-García-Hidalgo C, Alarcón-Blanco P, Gutiérrez-Fernández J. Male genitourinary infections by Corynebacterium glucuronolyticum. A review and clinical experience. Revista Espanola De Quimioterapia : Publicacion Oficial De La Sociedad Espanola De Quimioterapia. 2019; 32: 479–484.
[40] Onywera H, Williamson AL, Ponomarenko J, Meiring TL. The Penile Microbiota in Uncircumcised and Circumcised Men: Relationships With HIV and Human Papillomavirus Infections and Cervicovaginal Microbiota. Frontiers in Medicine. 2020; 7: 383. https://doi.org/10.3389/fmed.2020.00383
[41] Okwelogu SI, Ikechebelu JI, Agbakoba NR, Anukam KC. Microbiome Compositions From Infertile Couples Seeking *In Vitro* Fertilization, Using 16S rRNA Gene Sequencing Methods: Any Correlation to Clinical Outcomes? Frontiers in Cellular and Infection Microbiology. 2021; 11: 709372. https://doi.org/10.3389/fcimb.2021.709372
[42] Atmoko W, Savira M, Shah R, Chung E, Agarwal A. Isolated teratozoospermia: revisiting its relevance in male infertility: a narrative review. Translational Andrology and Urology. 2024; 13: 260–273. https://doi.org/10.21037/tau-23-397
[43] Mehta RH, Sridhar H, Vijay Kumar BR, Anand Kumar TC. High incidence of oligozoospermia and teratozoospermia in human semen infected with the aerobic bacterium Streptococcus faecalis. Reproductive Biomedicine Online. 2002; 5: 17–21. https://doi.org/10.1016/s1472-6483(10)61591-x
[44] Monteiro C, Marques PI, Cavadas B, Damião I, Almeida V, Barros N, et al. Characterization of microbiota in male infertility cases uncovers differences in seminal hyperviscosity and oligoasthenoteratozoospermia possibly correlated with increased prevalence of infectious bacteria. American Journal of Reproductive Immunology (New York, N.Y. : 1989). 2018; 79: e12838. https://doi.org/10.1111/aji.12838
[45] Weng SL, Chiu CM, Lin FM, Huang WC, Liang C, Yang T, et al. Bacterial communities in semen from men of infertile couples: metagenomic sequencing reveals relationships of seminal microbiota to semen quality. PloS One. 2014; 9: e110152. https://doi.org/10.1371/journal.pone.0110152
[46] Chatzokou D, Tsarna E, Davouti E, Siristatidis CS, Christopoulou S, Spanakis N, et al. Semen Microbiome, Male Infertility, and Reproductive Health. International Journal of Molecular Sciences. 2025; 26: 1446. https://doi.org/10.3390/ijms26041446
[47] Grande G, Graziani A, De Toni L, Garolla A, Ferlin A. Male Tract Microbiota and Male Infertility. Cells. 2024; 13: 1275. https://doi.org/10.3390/cells13151275
[48] He J, Ma M, Xu Z, Guo J, Chen H, Yang X, et al. Association between semen microbiome disorder and sperm DNA damage. Microbiology Spectrum. 2024; 12: e0075924. https://doi.org/10.1128/spectrum.00759-24
[49] Dutta S, Sengupta P, Izuka E, Menuba I, Jegasothy R, Nwagha U. Staphylococcal infections and infertility: mechanisms and management. Molecular and Cellular Biochemistry. 2020; 474: 57–72. https://doi.org/10.1007/s11010-020-03833-4
[50] Fraczek M, Kurpisz M. Mechanisms of the harmful effects of bacterial semen infection on ejaculated human spermatozoa: potential inflammatory markers in semen. Folia Histochemica et Cytobiologica. 2015; 53: 201–217. https://doi.org/10.5603/fhc.a2015.0019
[51] Agarwal A, Rana M, Qiu E, AlBunni H, Bui AD, Henkel R. Role of oxidative stress, infection and inflammation in male infertility. Andrologia. 2018; 50: e13126. https://doi.org/10.1111/and.13126
[52] Moretti E, Figura N, Campagna MS, Gonnelli S, Iacoponi F, Collodel G. Sperm Parameters and Semen Levels of Inflammatory Cytokines in Helicobacter pylori-infected Men. Urology. 2015; 86: 41–46. https://doi.org/10.1016/j.urology.2015.02.068
[53] Tvrdá E, Lovíšek D, Gálová E, Schwarzová M, Kováčiková E, Kunová S, et al. Possible Implications of Bacteriospermia on the Sperm Quality, Oxidative Characteristics, and Seminal Cytokine Network in Normozoospermic Men. International Journal of Molecular Sciences. 2022; 23: 8678. https://doi.org/10.3390/ijms23158678
[54] Dehghan Marvast L, Aflatoonian A, Talebi AR, Ghasemzadeh J, Pacey AA. Semen inflammatory markers and Chlamydia trachomatis infection in male partners of infertile couples. Andrologia. 2016; 48: 729–736. https://doi.org/10.1111/and.12501
[55] Tjagur S, Mändar R, Poolamets O, Pomm K, Punab M. *Mycoplasma genitalium* Provokes Seminal Inflammation among Infertile Males. International Journal of Molecular Sciences. 2021; 22: 13467. https://doi.org/10.3390/ijms222413467
[56] Moretti E, Cosci I, Spreafico A, Serchi T, Cuppone AM, Collodel G. Semen characteristics and inflammatory mediators in infertile men with different clinical diagnoses. International Journal of Andrology. 2009; 32: 637–646. https://doi.org/10.1111/j.1365-2605.2008.00911.x
[57] Pérez-Soto E, Oros-Pantoja R, Fernández-Martínez E, Carbonell-Campos JM, Sánchez Monroy V. Seminal pro-inflammatory cytokines and pH are affected by *Chlamydia* infection in asymptomatic patients with teratozoospermia. Central-European Journal of Immunology. 2021; 46: 76–81. https://doi.org/10.5114/ceji.2021.105247
[58] AL Hadrawi KK, Darweesh MF. Evaluation serum level of IL-17, IL-23 and IL-35 in patients with bacterial prostatitis in Najaf Province. AIP Conference Proceedings. 2024; 3092: 020008. https://doi.org/10.1063/5.0200466
[59] Qian L, Bian GR, Li HB, Zhou Y, Dong SD, Wang WJ, et al. Effects of Ureaplasma urealyticum Infection on Sperm Quality and Concentrations of Nitric Oxide and Cytokine in the Semen of Infertile Males. American Journal of Reproductive Immunology (New York, N.Y. : 1989). 2016; 75: 605–608. https://doi.org/10.1111/aji.12500
[60] Hakimi H, Zainodini N, Khorramdelazad H, Kazemi Arababadi M, Hassanshahi G. Seminal Levels of Pro-inflammatory (CXCL1, CXCL9, CXCL10) and Homeostatic (CXCL12) Chemokines in Men With Asymptomatic Chlamydia trachomatis Infection. Jundishapur Journal of Microbiology. 2014; 7: e11152. https://doi.org/10.5812/jjm.11152
[61] Qian L, Zhou Y, Du C, Wen J, Teng S, Teng Z. IL-18 levels in the semen of male infertility: semen analysis. International Journal

of Biological Macromolecules. 2014; 64: 190–192. https://doi.org/10.1016/j.ijbiomac.2013.12.005
[62] Paradisi R, Capelli M, Mandini M, Bellavia E, Flamigni C. Increased levels of interferon-gamma in seminal plasma of infertile men. Andrologia. 1996; 28: 157–161. https://doi.org/10.1111/j.1439-0272.1996.tb02775.x
[63] Mazzoli S, Cai T, Addonisio P, Bechi A, Mondaini N, Bartoletti R. Chlamydia trachomatis infection is related to poor semen quality in young prostatitis patients. European Urology. 2010; 57: 708–714. https://doi.org/10.1016/j.eururo.2009.05.015
[64] Raad G, Fakih F, Bazzi M, Massaad V, Nasrallah E, Yarkiner Z, et al. Lactobacillus plantarum secretions may exert a cryoprotective effect on human sperm motility: A prospective in vitro study. Andrology. 2023; 11: 1437–1450. https://doi.org/10.1111/andr.13433
[65] Paira DA, Olivera C, Tissera AD, Molina RI, Olmedo JJ, Rivero VE, et al. Ureaplasma urealyticum and Mycoplasma hominis urogenital infections associate with semen inflammation and decreased sperm quality. Journal of Leukocyte Biology. 2023; 113: 18–26. https://doi.org/10.1093/jleuko/qiac006
[66] Paira DA, Molina G, Tissera AD, Olivera C, Molina RI, Motrich RD. Results from a large cross-sectional study assessing Chlamydia trachomatis, Ureaplasma spp. and Mycoplasma hominis urogenital infections in patients with primary infertility. Scientific Reports. 2021; 11: 13655. https://doi.org/10.1038/s41598-021-93318-1
[67] Cheng C, Chen X, Song Y, Wang S, Pan Y, Niu S, et al. Genital mycoplasma infection: a systematic review and meta-analysis. Reproductive Health. 2023; 20: 136. https://doi.org/10.1186/s12978-023-01684-y
[68] Cools P. The role of Escherichia coli in reproductive health: state of the art. Research in Microbiology. 2017; 168: 892–901. https://doi.org/10.1016/j.resmic.2017.02.002
[69] Schulz M, Sánchez R, Soto L, Risopatrón J, Villegas J. Effect of Escherichia coli and its soluble factors on mitochondrial membrane potential, phosphatidylserine translocation, viability, and motility of human spermatozoa. Fertility and Sterility. 2010; 94: 619–623. https://doi.org/10.1016/j.fertnstert.2009.01.140
[70] Eley A, Pacey AA, Galdiero M, Galdiero M, Galdiero F. Can Chlamydia trachomatis directly damage your sperm? The Lancet. Infectious Diseases. 2005; 5: 53–57. https://doi.org/10.1016/S1473-3099(04)01254-X
[71] Singer M, Ouburg S. Effect of cytokine level variations in individuals on the progression and outcome of bacterial urogenital infections–a meta-analysis. Pathogens and Disease. 2016; 74: ftv126. https://doi.org/10.1093/femspd/ftv126
[72] Wang S, Liu L, Zhang A, Song Y, Kang J, Liu X. Association between human papillomavirus infection and sperm quality: A systematic review and a meta-analysis. Andrologia. 2021; 53: e14034. https://doi.org/10.1111/and.14034
[73] Lampiao F, du Plessis SS. TNF-alpha and IL-6 affect human sperm function by elevating nitric oxide production. Reproductive Biomedicine Online. 2008; 17: 628–631. https://doi.org/10.1016/s1472-6483(10)60309-4
[74] Lang T, Hudemann C, Tchatalbachev S, Stammler A, Michel V, Aslani F, et al. Uropathogenic Escherichia coli modulates innate immunity to suppress Th1-mediated inflammatory responses during infectious epididymitis. Infection and Immunity. 2014; 82: 1104–1111. https://doi.org/10.1128/IAI.01373-13
[75] D'Cruz OJ, Vassilev AO, Uckun FM. Members of the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway are present and active in human sperm. Fertility and Sterility. 2001; 76: 258–266. https://doi.org/10.1016/s0015-0282(01)01896-9
[76] Sagare-Patil V, Modi D. Progesterone activates Janus Kinase 1/2 and activators of transcription 1 (JAK1-2/STAT1) pathway in human spermatozoa. Andrologia. 2013; 45: 178–186. https://doi.org/10.1111/j.1439-0272.2012.01332.x
[77] Alnajem A, Al-Maghrebi M. The Regulatory Effects of JAK2/STAT3 on Spermatogenesis and the Redox Keap1/Nrf2 Axis in an Animal Model of Testicular Ischemia Reperfusion Injury. Cells. 2023; 12: 2292. https://doi.org/10.3390/cells12182292
[78] Kyrgiafini MA, Kontse C, Chatziparasidou A, Mamuris Z. Whole-genome profile of Greek patients with asthenozoospermia: Identification of candidate variants and genes. In Proceedings of the 2nd International Electronic Conference on Genes (pp. 11–13). MDPI: Basel, Switzerland. 2024.
[79] Wang J, Gong X, Meng F, Deng S, Dai H, Bao B, et al. Biological Network Model of Effect of Chronic Intermittent Hypoxia on Spermatogenesis in Rats. Medical Science Monitor : International Medical Journal of Experimental and Clinical Research. 2020; 26: e925579. https://doi.org/10.12659/MSM.925579
[80] Morris R, Kershaw NJ, Babon JJ. The molecular details of cytokine signaling via the JAK/STAT pathway. Protein Science : a Publication of the Protein Society. 2018; 27: 1984–2009. https://doi.org/10.1002/pro.3519
[81] Laflamme J, Akoum A, Leclerc P. Induction of human sperm capacitation and protein tyrosine phosphorylation by endometrial cells and interleukin-6. Molecular Human Reproduction. 2005; 11: 141–150. https://doi.org/10.1093/molehr/gah142
[82] Perdichizzi A, Nicoletti F, La Vignera S, Barone N, D'Agata R, Vicari E, et al. Effects of tumour necrosis factor-alpha on human sperm motility and apoptosis. Journal of Clinical Immunology. 2007; 27: 152–162. https://doi.org/10.1007/s10875-007-9071-5
[83] Redgrove KA, McLaughlin EA. The Role of the Immune Response in Chlamydia trachomatis Infection of the Male Genital Tract: A Double-Edged Sword. Frontiers in Immunology. 2014; 5: 534. https://doi.org/10.3389/fimmu.2014.00534
[84] Hedger MP. Toll-like receptors and signalling in spermatogenesis and testicular responses to inflammation–a perspective. Journal of Reproductive Immunology. 2011; 88: 130–141. https://doi.org/10.1016/j.jri.2011.01.010
[85] Umehara T, Yamanaka T, Shimada M. Toll-like receptors in mammalian sperm. Reproductive Medicine and Biology. 2025; 24: e12651. https://doi.org/10.1002/rmb2.12651
[86] Martínez-Prado E, Camejo Bermúdez MI. Expression of IL-6, IL-8, TNF-alpha, IL-10, HSP-60, anti-HSP-60 antibodies, and anti-sperm antibodies, in semen of men with leukocytes and/or bacteria. American Journal of Reproductive Immunology (New York, N.Y. : 1989). 2010; 63: 233–243. https://doi.org/10.1111/j.1600-0897.2009.00786.x
[87] Dutta S, Sengupta P, Slama P, Roychoudhury S. Oxidative Stress, Testicular Inflammatory Pathways, and Male Reproduction. International Journal of Molecular Sciences. 2021; 22: 10043. https://doi.org/10.3390/ijms221810043
[88] Hagan S, Khurana N, Chandra S, Abdel-Mageed AB, Mondal D, Hellstrom WJG, et al. Differential expression of novel biomarkers (TLR-2, TLR-4, COX-2, and Nrf-2) of inflammation and oxidative stress in semen of leukocytospermia patients. Andrology. 2015; 3: 848–855. https://doi.org/10.1111/andr.12074
[89] Parida R. Human MOSPD2: A bacterial Lmb mimicked autoantigen is involved in immune infertility. Journal of Translational Autoimmunity. 2019; 1: 100002. https://doi.org/10.1016/j.jtauto.2019.100002
[90] Henkel R. Leukocytospermia and/or Bacteriospermia: Impact on Male Infertility. Journal of Clinical Medicine. 2024; 13: 2841. https://doi.org/10.3390/jcm13102841
[91] Loveland KL, Klein B, Pueschl D, Indumathy S, Bergmann M, Loveland BE, et al. Cytokines in Male Fertility and Reproductive Pathologies: Immunoregulation and Beyond. Frontiers

in Endocrinology. 2017; 8: 307. https://doi.org/10.3389/fendo.2017.00307

[92] Potiris A, Moustakli E, Trismpioti E, Drakaki E, Mavrogianni D, Matsas A, et al. From Inflammation to Infertility: How Oxidative Stress and Infections Disrupt Male Reproductive Health. Metabolites. 2025; 15: 267. https://doi.org/10.3390/metabo15040267

[93] Lang T, Dechant M, Sanchez V, Wistuba J, Boiani M, Pilatz A, et al. Structural and functional integrity of spermatozoa is compromised as a consequence of acute uropathogenic E. coli-associated epididymitis. Biology of Reproduction. 2013; 89: 59. https://doi.org/10.1095/biolreprod.113.110379

[94] Zeyad A, Hamad MF, Hammadeh ME. The effects of bacterial infection on human sperm nuclear protamine P1/P2 ratio and DNA integrity. Andrologia. 2018; 50: 10.1111/and.12841. https://doi.org/10.1111/and.12841

[95] Boguen R, Treulen F, Uribe P, Villegas JV. Ability of Escherichia coli to produce hemolysis leads to a greater pathogenic effect on human sperm. Fertility and Sterility. 2015; 103: 1155–1161. https://doi.org/10.1016/j.fertnstert.2015.01.044

[96] Lysiak JJ. The role of tumor necrosis factor-alpha and interleukin-1 in the mammalian testis and their involvement in testicular torsion and autoimmune orchitis. Reproductive Biology and Endocrinology : RB&E. 2004; 2: 9. https://doi.org/10.1186/1477-7827-2-9

[97] Saxena P, Soni R, Randhawa VS, Singh N. Can Seminal IL-8 Level Be Used as a Marker of Leukocytospermia and Does It Have Any Correlation with Semen Parameters in Infertile Couples? Journal of Obstetrics and Gynaecology of India. 2019; 69: 451–456. https://doi.org/10.1007/s13224-018-1188-3

[98] Kim YK, Shin JS, Nahm MH. NOD-Like Receptors in Infection, Immunity, and Diseases. Yonsei Medical Journal. 2016; 57: 5–14. https://doi.org/10.3349/ymj.2016.57.1.5

[99] Tavalaee M, Rahmani M, Drevet JR, Nasr-Esfahani MH. The NLRP3 inflammasome: molecular activation and regulation in spermatogenesis and male infertility; a systematic review. Basic and Clinical Andrology. 2022; 32: 8. https://doi.org/10.1186/s12610-022-00157-9

[100] Havrylyuk A, Chopyak V, Boyko Y, Kril I, Kurpisz M. Cytokines in the blood and semen of infertile patients. Central-European Journal of Immunology. 2015; 40: 337–344. https://doi.org/10.5114/ceji.2015.54596

[101] Qian L, Shi Q, Gu Y, Song J, Zhou M, Hua M. The relationship between IL-17 and male infertility: Semen analysis. African Journal of Microbiology Research. 2012; 6: 5672–5677. https://doi.org/10.5897/AJMR12.696