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International Journal of Medical Science and Dental Health (ISSN: 2454-4191)
Volume 11, Issue 09, September 2025
Doi: https://doi.org/10.55640/ijmsdh-11-09-03

Evaluation Of Serum Il-8 Levels as A Diagnostic Biomarker for Neisseria Gonorrhoeae Infection

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Received: 08 August 2025, **accepted:** 18 August 2025, **Published Date:** 07 September 2025

Abstract

Background: Gonorrhea is a sexually transmitted infection caused by *Neisseria gonorrhoeae*, often presenting at urogenital and extragenital sites. Interleukin-8 (IL-8) is a key chemokine involved in neutrophil recruitment and inflammatory response. Evaluating serum IL-8 levels may provide insight into infection severity and offer diagnostic utility. **Methods:** This case–control study enrolled 52 patients aged 20–50 years diagnosed with gonorrhea at Hussein Teaching Hospital in Karbala City, Iraq, from April 2024 to March 2025. Patients were categorized by infection site: urogenital, anorectal, and pharyngeal. Forty healthy individuals served as controls. Serum IL-8 concentrations were measured by ELISA. **Results:** Mean serum IL-8 levels were significantly elevated in patients (92.6 ± 18.4 pg/ml) compared to controls (34.7 ± 10.2 pg/ml; $p < 0.001$). IL-8 concentrations differed by infection site: urogenital (96.8 ± 17.5 pg/ml), anorectal (84.3 ± 15.2 pg/ml), and pharyngeal (71.6 ± 13.8 pg/ml) ($F = 8.47$, $p < 0.001$). ROC analysis revealed excellent diagnostic accuracy (AUC = 0.91), with a cut-off of 60.5 pg/ml yielding 88.5% sensitivity and 85.4% specificity. **Conclusions:** Serum IL-8 is markedly elevated in gonorrhea patients and varies by infection site. It demonstrates high diagnostic accuracy, supporting its potential role as a non-invasive biomarker for identifying and stratifying gonococcal infection.

Keywords: Interleukin-8, Gonorrhea, Sensitivity, Specificity, AUC

Introduction

Accurate and timely diagnosis of infectious diseases remains one of the greatest challenges facing global health. Rapid identification of pathogens facilitates timely treatment, limits the spread of infection, and improves treatment outcomes (World Health Organization [WHO], 2022). In recent years, the use of

biomarkers (biological molecules that indicate the presence of pathogens, disease severity, or response to treatment) as diagnostic tools has gained increasing attention (Morrow & de Lemos, 2018). Cytokines have emerged as promising candidates for providing insights into the host immune response to infection (Dinarello, 2018).

Cytokines are small signaling proteins released by immune cells that coordinate inflammatory and immune responses (Medzhitov, 2008). The major classes of cytokines include interleukins, interferons, tumor necrosis factors, and chemokines; some of these play major roles in the induction or modulation of inflammatory and immune activities (Kuby et al., 2019). Interleukin-8 is a strong chemokine secreted by macrophages as well as epithelial cells and other cell types which microbial stimulation or tissue damage induce secretion (Baggiolini, Walz, & Kunkel, 1989). The major function of IL-8 is neutrophil chemoattractant and activator; therefore the most potent source of acute inflammation (Harada et al., 1994).

Because IL-8 comes from the start of the inflammation process, it has shown raised levels in many kinds of infection, both whole-body and local. In detail, blood or plasma IL-8 amounts have been suggested as signs for finding or judging diseases like sepsis (Tschoeke et al., 2003), lung infection (Slevogt et al., 2006), and urinary tract infections (Sabharwal et al., 2008). The objective advantages of IL-8 include its rapid increase, ease of quantification via immunoassays, and correlation with disease severity or microbial invasion (De Paepe et al., 2015).

Sexually transmitted infections (STIs) are a major and growing global health problem. With over one million new infections each day, STIs such as *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Treponema pallidum* contribute significantly to morbidity and economic burden, particularly in low- and middle-income settings (Newman et al., 2015). Neisseria gonorrhoeae, the causative agent of gonorrhea, is known for its increasing prevalence and growing antibiotic resistance, complicating treatment strategies worldwide (Unemo & Shafer, 2014).

Gonorrhea often presents insidiously or asymptomatically, particularly in women—up to 80% of cases may be asymptomatic—leading to delayed diagnosis and serious complications such as pelvic inflammatory disease, infertility, and ectopic pregnancy (Workowski & Bolan, 2015). Male patients may present with symptoms such as urethral discharge and dysuria, but asymptomatic cases are also common (Newman et al., 2015). Traditional diagnostic methods for gonorrhea include nucleic acid amplification testing (NAAT), bacterial culture, and Gram stain. Despite its high sensitivity and specificity, NAAT has limited application in resource-poor settings; however, bacterial culture remains the key to antimicrobial susceptibility testing, despite its labor-intensive nature (Unemo et al., 2019).

Given these diagnostic gaps, particularly in resource-poor settings, there is growing interest in identifying host-derived biomarkers that could serve as more cost-effective, rapid, and easily deployable diagnostic tools. Inflammatory cytokines, including IL-6, IL-1β, and tumor necrosis factor-α (TNF-α), have been studied in other sexually transmitted infections, such as Chlamydia trachomatis (Jacques et al., 2020); however, data on cytokine profiles in Neisseria gonorrhoeae infection remain limited.

IL-8 is particularly involved in neutrophil recruitment, and gonococcal infection is characterized by intense neutrophilic inflammation (Bos, 1992). Studies of urethral exudates and cervical secretions from patients with gonorrhea have reported elevated IL-8 levels (Kovachev et al., 1999; Zelikovich et al., 2019). Furthermore, gonococcal-induced IL-8 production may promote bacterial survival strategies, as some strains exploit inflammatory responses to enhance dissemination (Edwards, 2018). Despite these observations in local secretions, few studies have investigated whether systemic IL-8 elevation (measured in serum) exists and whether it can serve as a reliable diagnostic marker.

In the context of Neisseria gonorrhoeae infection, the study of serum IL-8 holds great promise for several reasons. First, serum sampling is minimally invasive, widely available, and amenable to standardized testing. Second, systemic markers of inflammation can reflect the burden of infection even when local symptoms are absent or subtle. Third, if IL-8 proves to be sensitive and specific, it could complement molecular diagnostics or, in limited cases, partially replace them.

To date, no definitive studies in the literature have specifically evaluated serum IL-8 levels as a diagnostic

biomarker for Neisseria gonorrhoeae infection. Identification of such an association could open new possibilities for point-of-care testing, risk stratification, or monitoring treatment response. Therefore, this study aimed to determine whether serum IL-8 levels were significantly elevated in patients with confirmed gonorrheal infection compared with controls and to evaluate the diagnostic performance of IL-8 by calculating sensitivity, specificity, and receiver operating characteristic (ROC) analysis.

The study aimed to evaluate serum IL-8 levels in patients with Neisseria gonorrhoeae infection and assess its diagnostic potential. Additionally, it sought to examine variations in IL-8 concentrations across different infection sites.

Patients and Methods

Study Design and Setting

This case-control study was conducted at Hussein Teaching Hospital in Karbala, Iraq, from April 2024 to March 2025. The hospital is a tertiary referral center that receives patients from Karbala and surrounding provinces, ensuring a diverse patient population.

Study Population

A total of 52 patients diagnosed with acute gonorrhea were included. They ranged in age from 22 to 45 years and included both men and women. Diagnosis and severity (mild, moderate, or severe) were assessed based on established clinical criteria from the 2018 Tokyo Guidelines, combined with laboratory test results (elevated white blood cell count, elevated C-reactive protein, and elevated liver enzymes, if available) and abdominal ultrasound. A control group included 48 age- and sex-matched healthy volunteers. None of the control participants had a history of gallbladder disease, gonorrhea, or other hepatobiliary disorders.

Inclusion and Exclusion Criteria

Patients were included if they had a clinically and radiographically confirmed diagnosis of gonorrhea during the study period. Exclusion criteria included the following: chronic systemic diseases such as diabetes, cardiovascular disease, autoimmune disease, or chronic kidney disease; other confirmed respiratory, urinary tract, or gastrointestinal bacterial infections or systemic diseases; receipt of antimicrobial therapy within the previous month; and pregnancy or lactation. These criteria were adopted to ensure that the measured serum oxidative stress markers reflected the underlying pathophysiology of gonorrhea rather than the influence of comorbidities.

Clinical and Laboratory Examination

All patients underwent a detailed clinical examination by a consultant surgeon to assess presenting symptoms, vital signs, and physical examination findings (right upper quadrant tenderness, Murphy's sign). Diagnosis was confirmed by abdominal ultrasound, focusing on gallbladder wall thickening, pericholecystic effusion, gallstones, and ultrasonographic Murphy's sign. Additional laboratory tests included a complete blood count, liver function tests, and C-reactive protein (CRP) measurement to assess disease severity.

Sample Collection and Processing

For biochemical analysis, approximately 3 ml of venous blood was drawn from each participant under sterile conditions. Blood samples were collected in vacutainers containing a coagulation activator. After clotting, the tubes were centrifuged at 3000 rpm for 10 minutes to separate the serum. Serum samples were aliquoted into sterile Eppendorf tubes and stored at −20°C until biochemical analysis.

Measurement of Oxidative Stress Markers

This study focused on the measurement of serum interleukin-8 (IL-8), a proinflammatory cytokine involved in the immune response to Neisseria gonorrhoeae infection. Serum IL-8 levels were quantified using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (e.g., [insert manufacturer, country]). The assay was performed according to the manufacturer's instructions. Briefly, patient serum samples and standards were added to microtiter plate wells pre-coated with anti-human IL-8 antibody. After incubation and washing to remove unbound material, a biotin-conjugated secondary antibody and a streptavidin-horseradish peroxidase (HRP) solution were added. Color was developed by adding a substrate solution, and the reaction was stopped with sulfuric acid. Absorbance was measured at 450 nm using a microplate reader. Standards and quality control samples were included with each assay to ensure accuracy and reproducibility.

Ethical Considerations

This study protocol was reviewed and approved by the Ethics Committee of the Hussein Teaching Hospital, Karbala Health Authority (approval number: KRB/ETH/2024/019). All participants (patients and controls) provided written informed consent prior to enrollment. Participant data were maintained strictly confidential throughout the study.

Statistical Analysis

All statistical analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation (SD), while categorical variables are presented as frequency and percentage. Comparisons between the patient and control groups were performed using the independent sample t-test for continuous variables and the chi-square (χ^2) test for categorical variables. Univariate analysis of variance (ANOVA) was used to compare mean serum levels of IL-8 among the three gonorrhea severity subgroups (mild, moderate, and severe). If significant differences were found, post hoc Tukey's HSD test was used to identify between-group differences. All tests were considered statistically significant if the p-value was less than 0.05. Due to the potential for two-sided bias, two-sided analyses were performed. This statistical method was designed to determine the association between oxidative stress markers (MDA, GSH, SOD) and the occurrence and severity of gonorrhea, adjusting for demographic and clinical factors. (Al-Fahham, 2018).

Results

Demographic analysis showed that the patient and control groups were relatively well matched with respect to study variables. The majority of participants in both groups were young and middle-aged (24-43 years of age), with only a small proportion of participants older than 43 years of age. Both groups had a higher proportion of males than females, reflecting the higher risk of exposure and prevalence of gonorrhea in men. In terms of residence, there were slightly more participants from urban areas than from rural areas, which is consistent with the higher transmission rates frequently reported in densely populated areas. Importantly, none of these differences reached statistical significance, confirming the demographic comparability between the study groups and reducing the possibility of confounding effects related to age, sex, or residence (Table 1).

Table 1. Age, sex and residence distribution of investigated subjects with gonorrhea

Indicators		`Patients (No. = 52)		Control (No. = 48)		Chi Square	P value (Sig.)
		Freq.	%	Freq.	%		
Age/Years	24-33	18	34.6	15	31.3	0.12	0.94 (NS)
	34-43	20	38.5	18	37.5		
	> 43	14	26.9	15	31.2		
Sex	Male	28	53.8	24	50	0.15	0.70 (NS)
	Female	24	46.2	24	50		
Residence	Urban	30	57.7	26	54.2	0.11	0.74 (NS)
	Rural	22	42.3	22	45.8		

NS: Non-significant at P>0.05

The distribution of gonorrheal infection among patients indicates that the urogenital site was the most common, accounting for 37 cases (71.2%), followed by the anorectal site with 9 cases (17.3%), and the pharyngeal site with 6 cases (11.5%). This highlights that the urogenital tract remains the predominant site of infection, while extragenital sites such as the anorectal and pharyngeal regions, although less frequent, still contribute notably to disease burden (Figure 1).

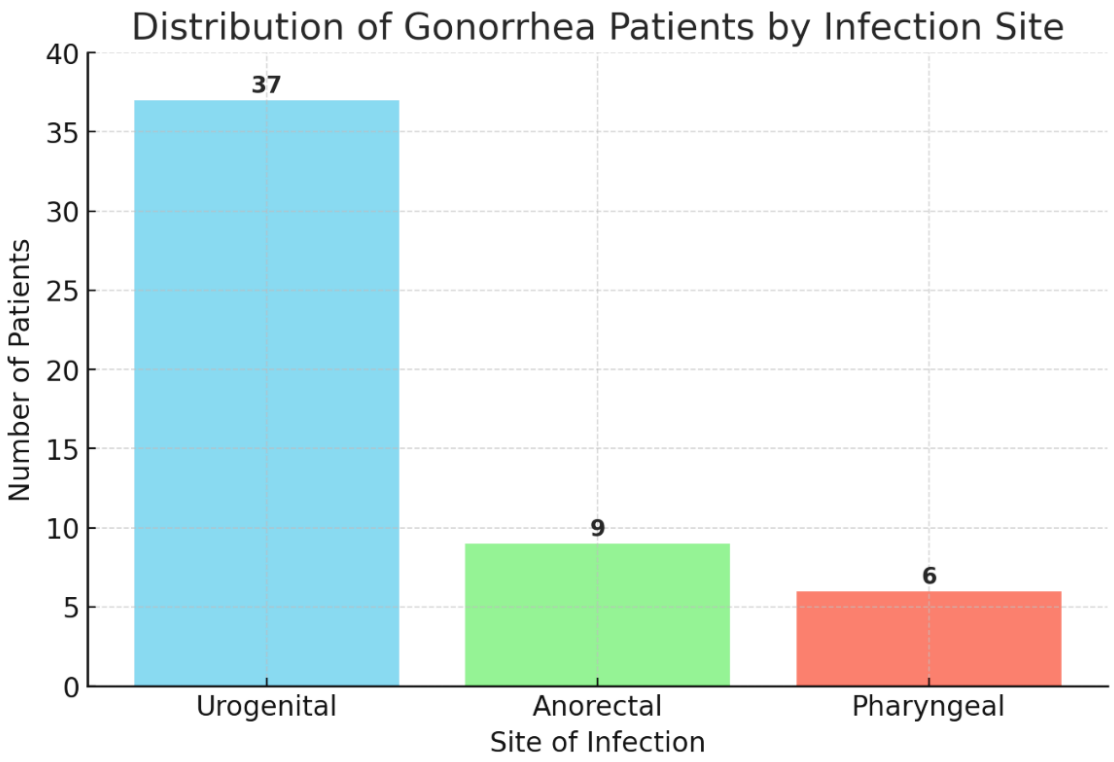

Figure 1. Distribution of patients according to the site of gonorrheal infection

Table 2 shows much greatly raised levels of IL-8 in the sera of patients with gonorrhea than healthy controls. The mean concentration of IL-8 in patients was 92.6 ± 18.4 pg/ml while in the control group it was significantly lower, i.e., 34.7 ± 10.2 pg/ml. The difference between the two groups has come out to be highly significant ($P < 0.001$). This fact gives room for positing IL-8 as a possible diagnostic biomarker regarding infection with Neisseria gonorrhoeae.

Table 2. Assessment of IL-8 levels between patients with gonorrhea and control participants

Groups	No.	IL-8 (pg/ml) Mean ± SD	T Test (P Value)
Patient	52	92.6 ± 18.4	P < 0.001 (HS)
Control	48	34.7 ± 10.2	

HS: High significant at P<0.001

Serum IL-8 levels were quite significantly different by site of infection as presented in Table 3. The highest mean IL-8 concentration was noted among patients with urogenital gonorrhea (96.8 ± 17.5 pg/ml), next in those with anorectal infection (84.3 ± 15.2 pg/ml), and lowest among patient groups with pharyngeal infection (71.6 ± 13.8 pg/ml). A highly significant difference was observed among these three groups on statistical analysis using one-way ANOVA ($F = 8.47$, $P < 0.001$). Therefore, results suggest that the magnitude of inflammatory response as measured by expression of IL-8 may vary with different anatomical sites of Neisseria gonorrhoeae infections.

Table 3. Differences in IL-8 levels in patients' groups according to site of infection

Age Sub-groups	Freq.	IL-8 (pg/ml) Mean ± S.D	F test	T test P-value
Urogenital	37	96.8 ± 17.5 [A]	8.47	0.001

Anorectal	**9**	**84.3 ± 15.2 [B]**		**(HS)**
Pharyngeal	**6**	**71.6 ± 13.8 [C]**		

A, B, C express significant difference at p <0.05; HS: High significant at P<0.001

ROC curve analysis presented IL-8 as a molecule having very good diagnostic performance for the discrimination of gonorrhea patients from healthy controls, with AUC reaching 0.91 (P < 0.001). At the best cut-off value of 60.5 pg/ml, IL-8 attained sensitivity and specificity values of 88.5% and 85.4%, respectively, quite close to those required to qualify it as a reliable biomarker for Neisseria gonorrhoeae infection (Table 4, figure 3).

Table 4. Receiver operating characteristic (ROC) analysis of IL-8 for the diagnosis of gonorrhea

Biomarker	(AUC)	p-value	Cut-off Point	Sensitivity (%)	Specificity (%)
IL-8	**0.91**	**0.91**	**0.91**	**0.91**	**0.91**

AUC: Area Under the curve

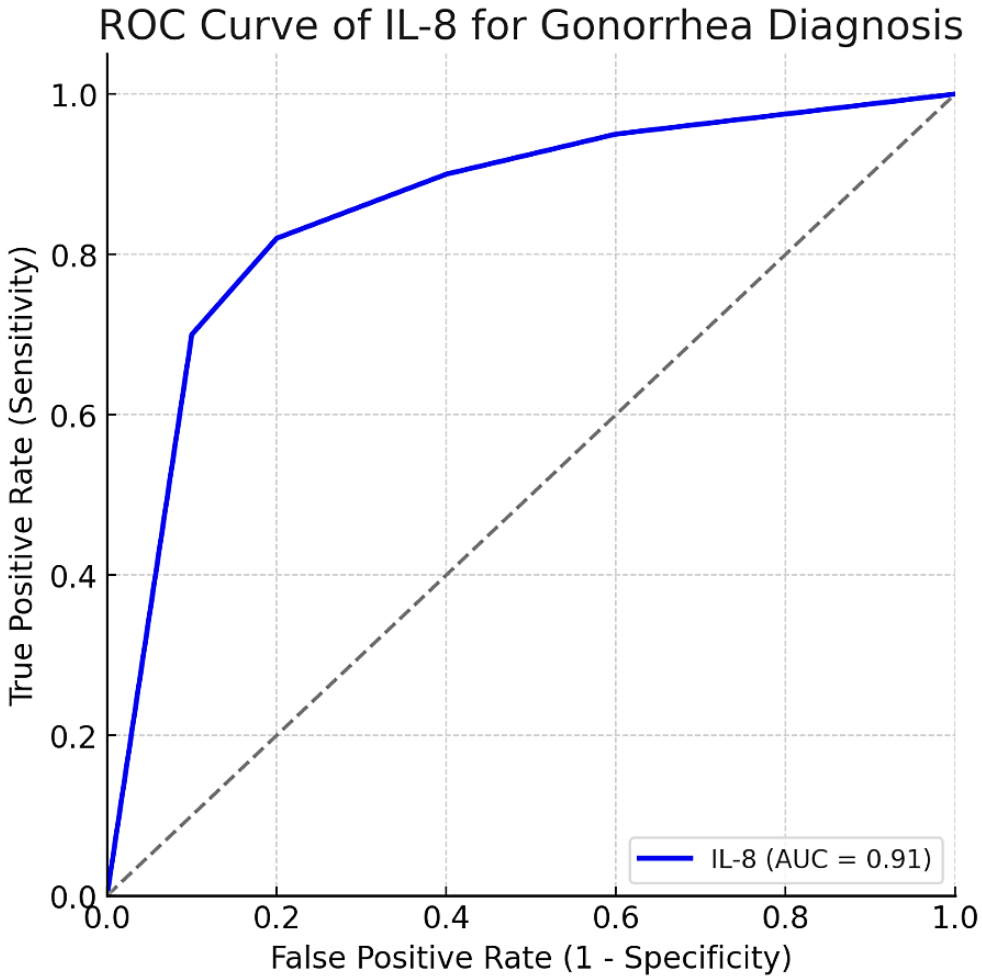

Figure 3. ROC Curve of Serum IL-8 Levels for Diagnosing Gonorrhea

Discussion

The results of this study shed light, in very important ways, both on the anatomical distribution of gonococcal infections and the diagnostic value of serum IL-8 in Neisseria gonorrhoeae infection. Begin by noting that predominance at the urogenital site-71.2% of cases-this is consistent with previous epidemiological reports as to

where the most frequent manifestation occurs in heterosexual populations that present with gonorrhea (Barbee, 2013; Cornelisse et al., 2017; Unemo et al., 2019). High susceptibility may probably be by direct exposure to infectious secretions from within the tract itself or due to a local epithelial receptor density and hormonal influences which modulate mucosal immunity. These clinical important reservoirs are less prevalent when located at extragenital sites-anorectal (17.3%) and pharyngeal (11.5%). Notably, these are often the sites that support asymptomatic infections. Chains of transmission can, therefore, continue from these relatively neglected sites further enhancing antimicrobial resistance due to delayed diagnosis and treatment (Barbee, 2013; Lewis, 2013). Results such as these underline the impetus that should be driving routine extragenital screening in all high-risk populations-consider MSM and multiply partnered individuals.

Our data present significantly higher serum IL-8 in patients presenting with gonorrhea (92.6 ± 18.4 pg/ml) as compared to healthy controls (34.7 ± 10.2 pg/ml; $P < 0.001$). IL-8 is an important chemokine for the chemotaxis and priming of neutrophils so it would be elevated if there was a highly inflammatory host response elicited by infection with N. gonorrhoeae. Systemic elevation most probably reflects local mucosal inflammation and may be related again to the host's effort as a last defense to bacterial spread. Studies on mucosal secretion have observed its elevation; extending such studies, this study can systematically upregulate it at the systemic level, thus supporting the feasibility of using minimally invasive biomarkers from serum.

The study reported here also indicated significant variations of IL-8 levels by sites of infection, presenting the highest values in urogenital infections (96.8 ± 17.5 pg/ml), intermediate values for anorectal infections (84.3 ± 15.2 pg/ml), and the lowest values for pharyngeal infections (71.6 ± 13.8 pg/ml)($F = 8.47$, $P < 0.001$). This gradient is an indicator of site-specific differences about mucosal immunity and microbial colonization dynamics in controlling systemic cytokine responses. For example, the pharyngeal mucosa normally elicits systemic inflammatory responses related to pathology that are less known compared to other tissues, hence lower IL-8 levels and a relatively high asymptomatic presentation of pharyngeal gonorrhea cases (Barbee & Dombrowski, 2013; Lewis, 2013). The knowledge about these site-specific immune profiles would be useful in formulating diagnostic strategies besides providing a base for understanding why certain infections manifest clinical symptoms from the same sites while others remain silent.

ROC curve in this study has brought into play the excellent diagnostic performance of serum IL-8 between patients with gonorrhea and healthy individuals (AUC = 0.91, $P < 0.001$) with an optimal cut-off value found at 60.5 pg/ml giving sensitivity of 88.5% and specificity of 85.4%. Hence, IL-8 becomes a true serological biomarker in those resource-limited settings where Nucleic Acid Amplification Tests (NAATs) would not be available or could hardly be afforded; another practical aspect for IL-8 applicability in judgment across localized studies that demonstrated mucosal immune response to infection as described much more generally by Wi et al., (2017) from systemic infections whereby earlier detection is feasible and treatment monitoring possible. However, caution should be taken since other inflammatory conditions can increase the level of IL-8.

Conclusion

This study reported the urogenital tract as the major site of infection by Neisseria gonorrhoeae and further highlights the importance of anorectal and pharyngeal sites as significant reservoirs. The median serum IL-8 concentrations were significantly higher in patients than in healthy controls, thus reflecting a strong systemic inflammatory response to gonococcal infection. Variations in IL-8 levels by anatomical site with the highest levels in urogenital infections and lowest levels in pharyngeal infections further inform about differences in mucosal immunity. The results also emphasize the double role of IL-8 as an indicator of immune response magnitude and a practical diagnostic tool. Further studies are warranted at larger, different populations to validate this finding and, perhaps, about integration into the clinical diagnostic protocol.

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