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ORIGINAL ARTICLE

Comprehensive evaluation of hematospermia in patients with acute epididymitis compared to patients with isolated hematospermia

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Abstract

Background: Among the most commonly known causes of hematospermia are infections in the genitourinary tract, but no study exists that has comprehensively investigated hematospermia in patients with acute epididymitis.

Objectives: To assess the impact of hematospermia in patients with acute epididymitis and its association with clinical, microbiological, and semen parameters.

Materials and methods: Since May 2007, a total of 324 sexually active patients with acute epididymitis were recruited in a prospective cohort study. Patients received a comprehensive medical and sexual history, and clinical, sonographic, laboratory, and microbiological diagnostics. Antibiotic therapy was given according to European Association of Urology guidelines. Semen analysis was offered 14 days after the first presentation and initiation of therapy. Since 2013, a separate control group of 56 patients presenting with isolated hematospermia (= no other urogenital symptoms) was prospectively recruited, and differences between the groups were statistically evaluated.

Results: Of 324 patients with acute epididymitis, 50 patients (15%) had self-reported hematospermia. This occurred with a median of 24 h before the onset of scrotal symptoms and was associated with significantly elevated prostate-specific antigen levels compared to 274 patients without hematospermia (3.1 vs. 1.8 ng/ml, $p < 0.01$). The two most common etiological pathogens were *Escherichia coli* and *Chlamydia trachomatis*, and the bacterial spectrum was comparable in both epididymitis subgroups ($p = 0.859$). Semen analysis at 14 days still showed hematospermia in 24% of patients associated with massive leukocytospermia. Compared to the hematospermia control group, the two epididymitis subgroups showed significantly increased inflammation markers (pH, leukocytes, and elastase), reduced sperm concentration, and reduced levels of alpha-glucosidase and zinc (always $p < 0.01$).

Discussion and conclusion: In sexually active patients who develop acute epididymitis, self-reported hematospermia is evident in 15% of patients as early as one day before the onset of scrotal symptoms. Conversely, none of the 56 patients presenting with isolated hematospermia developed epididymitis within the next 4 weeks.

KEYWORDS
epididymitis, hematospermia, infertility, leukocytospermia, PSA, urogenital tract infection

1 | INTRODUCTION

Hematospermia is traditionally defined as the macroscopic presence of blood in semen. Even in earlier centuries, important physicians including Galen and Hippocrates have commented on this condition. The symptom causes anxiety in many patients who think of hematospermia as a sign of malignancy, hence up to that 76% of patients have been reported to seek medical advice after only one or two episodes were experienced.[1] The incidence of hematospermia is quite unclear, as most ejaculations during sexual intercourse go unnoticed. Nevertheless, recent insurance data from the United States report an incidence of 73.6 per 100,000 in 2018, with 0.08% of cases attributable to urological cancer.[2] This finding is consistent with another study that reported on a large prostate cancer screening population ($n = 26,126$) in which hematospermia was found to be 0.5%.[3] In a recent meta-analysis of a total of 20 studies, the etiology of hematospermia remained unknown in 52% of cases. Urogenital infections were of major relevance, but the studies were markedly heterogeneous with regard to the diagnostics performed so no reliable percentages could be calculated.[4] Only recently, the European Association of Urology (EAU) Guideline Group published a management algorithm for hematospermia.[5]

Acute epididymitis is the most common infection of the scrotum with an incidence of 100–250 per 100,000 males and year.[6,7] The leading etiological factor is the ascension of bacterial pathogens from the urethra to the epididymis. Therefore, the tail of the epididymis is affected first and further ascension leads to concomitant orchitis in up to 90% of cases.[8] Clinical signs are pain and swelling. Using modern molecular biological methods, the causative pathogens can be detected in urine samples in up to 89% of cases.[9] In the context of bacterial ascension, there is typically accompanying prostatitis, which is shown by increased prostate-specific antigen (PSA) values in the acute infection phase and which normalize again after antibiotic therapy.[8] Ejaculate analysis in acute situations is not recommended because of the pain symptoms and is not likely to bring any advantage compared to bacteriological urine diagnostics. However, in young males, a semen analysis in the follow-up is especially useful, since up to 40% of men have permanently impaired semen quality after acute epididymitis, with 10% even affected by azoospermia.[10] Interestingly, patients with acute epididymitis repeatedly self-report hematospermia in the context of the acute disease.

Given the often vague description of infection/inflammation as the etiology of hematospermia, the aim of the present study is to investigate the association between hematospermia and epididymitis comprehensively in a large prospective cohort study of patients with acute epididymitis.

2 | MATERIALS AND METHODS

2.1 | Study populations

After receiving approval from the institutional review board (Ref. No 100/7), we conducted a prospective cohort study in adults (>18 years) on the etiology, inflammation, impact on fertility, and clinical course of acute epididymitis at the Department of Urology, Pediatric Urology, and Andrology, Justus Liebig University Giessen, Germany (German clinical trials register: DRKS00003325) in the period from July 2007 to January 2023. The inclusion criterion was acute epididymitis, defined as onset within the last 2 weeks, enlarged epididymis on palpation typically associated with pain, and epididymal hyperemia in ultrasound.[9] A total of 570 consecutive patients with acute epididymitis were screened. Exclusion criteria were lack of informed consent or presence of scrotal disease other than epididymitis (e.g., testicular torsion and testicular tumor). The study was performed according to the Declaration of Helsinki. Altogether 530 patients were enrolled (Figure 1). Of these, 206 were excluded because of sexual inactivity during the last 6 months. Thus, the study population consisted of 50 patients who self-reported hematospermia before epididymitis and 274 patients who had not observed hematospermia. The patients with acute epididymitis presented initially at the emergency department without the need for a medical referral. A comprehensive medical and sexual history was obtained.

After the first reports of hematospermia among patients with acute epididymitis, the decision was made in 2013 to prospectively establish a control group of patients with self-reported hematospermia who presented to the urology outpatient clinic. For this purpose, the above-mentioned ethics approval was extended through an amendment in 2012 to include the hematospermia control group. Between October 2013 and January 2023, a total of 65 patients with isolated hematospermia (= no other urogenital symptoms) sought medical help, and from these, 56 patients were recruited for the hematospermia control group (Figure 1). These patients received a structured medical history including coexisting systemic diseases[5] and appropriate andrological/urological common diagnostics (blood analysis including PSA,

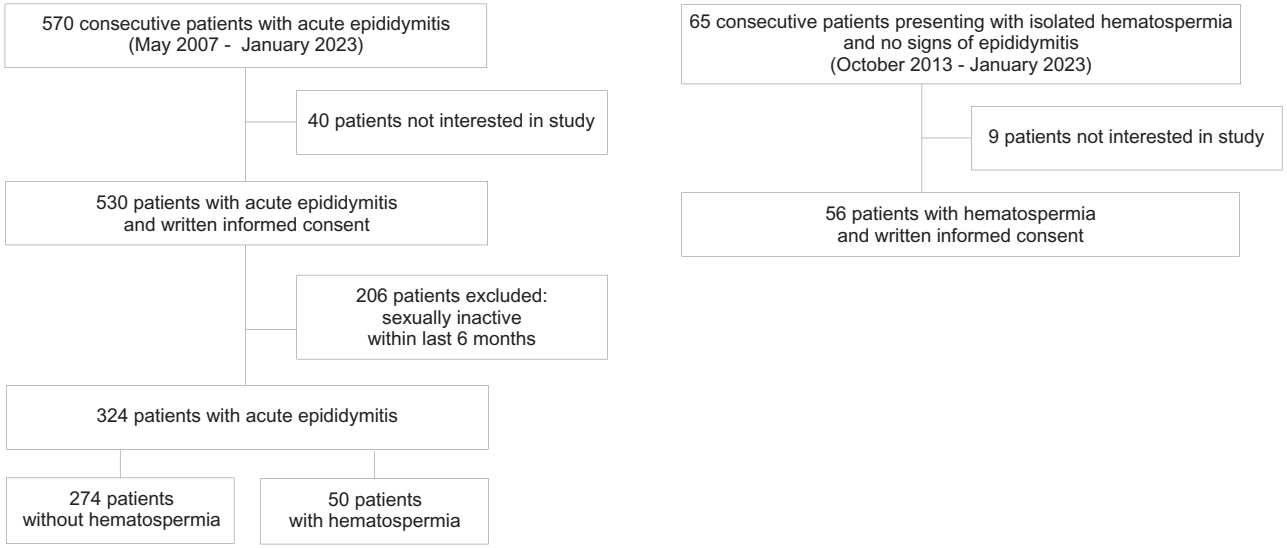

FIGURE 1 Overview of study populations.

urine culture, STI screening, ultrasound, semen analysis). Depending on the indication, individual patients also underwent a cystoscopy and/or a multiparametric magnetic resonance imaging of the prostate. Thus, the diagnostic approach used in this study is practically in line with the current recommendation of the EAU guideline group to clarify the etiology and identify possible treatment options.[5] Duration of follow-up was 4 weeks.

2.2 | Physical and ultrasound examination

By means of palpation, scrotal wall induration and the presence of epididymal and testicular pain were documented. Body temperature was measured in the ear and recorded in°C. In addition, scrotal contents and the prostate were evaluated by ultrasound in detail as described.[8,11]

2.3 | Laboratory methods

Routine blood samples were taken in all patients with epididymitis to determine white blood cell count (WBC), C-reactive protein (CRP), and serum PSA. Leukocyturia was determined by urine dipstick analysis with an automated quantitative urine particle analyzer (cobas u 411; Roche Diagnostics GmbH).

Follicle-stimulating hormone, luteinizing hormone, sex hormone-binding globulin, albumin, total testosterone, and estradiol were measured by routine laboratory methods in the central laboratory of our university hospital (ADVIA and ADVIA Centaur, Siemens Health Care). Free testosterone was calculated using Vermeulen's formula.[12] The blood for the determination of sex hormones was collected in the morning between 8 and 10 am directly before ejaculation.

Semen analysis was performed after sexual abstinence of 2–7 days and within 1 h of the collection according to WHO recommendations.[13,14] All analyses were performed in the same laboratory under stable methodological conditions. Of note, sperm concentration was measured using a Neubauer's improved hemocytometer; sperm motility was classified in WHO categories a–d, calculating progressive motility (PR; WHO 2010) as "a+b". Throughout the study, Shorr's staining of semen smears and strict criteria for defining normal sperm morphology were applied (WHO 2010; WHO 2021).[13–15] As part of standard processing, the concentration of peroxidase-positive leukocytes was determined (Leucoscreen; FertiPro). In addition, polymorphonuclear elastase reflecting local inflammation was measured by means of an enzyme-linked immunoassay in each semen sample (Milenia Biotec). Levels of neutral α-glucosidase and fructose (total enzymatic activity) at neutral pH were determined by spectrophotometrical methods.[16] Zinc was assessed using a commercially available kit (Zinc Kit). From each native semen sample, 100 μl were used for the microbiological work-up.

2.4 | Bacteriological and virological diagnostics

A standardized and extensive microbiological work-up was performed.[9] In brief, all patients and controls received urine cultures from mid-stream urine, and bacterial isolates were subsequently tested for antimicrobial susceptibility. In addition, all patients and controls with sexual activity within the last 6 months were screened for STIs by polymerase chain reaction (PCR) in the urogenital tract by either urethral swabs, first void urine, or post-prostatic massage urine. All patients who provided a semen sample also received an STI PCR from the ejaculate. PCR analysis was performed for the detection of *Mycoplasma genitalium*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, *Chlamydia trachomatis*, and *Neisseria gonorrhoeae* according to the manufacturer's recommendations (hyplex; Amplex BioSystems).[17] Negative urine samples (culture and STI PCR) were subjected to 16S rDNA analysis, as described.[18] Viral investigations were performed on

23 different viruses as real-time assays in all patients without detected bacterial pathogens ($n = 100$) in cryopreserved samples as described in detail elsewhere.[9]

2.5 | Therapy and follow-up

Patients with epididymitis were managed on an outpatient basis or hospitalized in cases with complicating factors as medically indicated.[19,20] In accordance with EAU/CDC guidelines, empiric therapy was initiated with levofloxacin 500 mg q.d. orally for 10 days. Additionally, hospitalized patients received cefotaxime 2 g t.i.d. intravenously.[19] Exceptions included patients with allergies, impaired renal function, contraindications, or previous bacteriological results that suggested a deviation from default choices. The primary antimicrobial regime was switched in a) cases of antimicrobial resistance detected by susceptibility testing; b) persistent disease; c) drug intolerance. Analgetic therapy, for example, diclofenac 75 mg b.i.d., was offered to all patients. Duration of hospitalization, as well as indications for surgery, were documented. After initial management, an early follow-up was scheduled after 14 days to assess the immediate response and a late follow-up after 3 months to assess microbiological cure and clinical outcome. Patients without a face-to-face late follow-up ($n = 113$) were interviewed by telephone to exclude treatment failure.

Patients in the control group suffering from hematospermia without epididymitis were categorized according to etiology after completion of all examinations and received adequate individualized treatment (e.g., antibiotic therapy, transurethral resection of the prostate, and radical prostatectomy).

2.6 | Statistical analysis

The demographics and characteristics of epididymitis patients with and without hematospermia were compared using the Mann-Whitney U test, Fisher's exact test, or Chi-square test, as indicated. When comparing both epididymitis subgroups with the hematospermia control group the Kruskal-Wallis test was applied. Variables were expressed accordingly as medians and interquartile range (IQR), or n and percentage. In order to assess which variables are associated with the occurrence of hematospermia in patients with acute epididymitis, a binary logistic regression (method: enter) was performed as a multivariable model. A value of $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS 27 for Windows (IBM GmbH).

3 | RESULTS

3.1 | Clinical data on epididymitis patients

In total, 324 patients with acute epididymitis who were sexually active within the last six months were recruited. Of these, 50 patients reported hematospermia prior to or in the setting of epididymitis, while 274 observed no hematospermia. The comprehensive clinical data from the first presentation are shown in Table 1. The comparison of both groups reveals that most of the clinical parameters are not significantly different. This is particularly important with regard to antibiotic pretreatment, which would represent a considerable bias. On the other hand, the interval between the last ejaculation and the time of presentation to the emergency unit, as well as the interval between the last ejaculation and the onset of scrotal pain are significantly different (in both cases $p < 0.001$). Figure 2 summarizes this relationship: the shorter the interval between the last ejaculation and the onset of scrotal pain, the more likely the occurrence of hematospermia (Figure 2). In addition, 23 patients (8%) without hematospermia had sonographic evidence of an abscess in the epididymis, whereas none of the patients were in the hematospermia subgroup ($p < 0.05$). Of note is the significantly higher median PSA value of 3.1 ng/ml in the subgroup with hematospermia, while it was 1.8 ng/ml in patients without hematospermia ($p < 0.001$). Binary logistic regression analysis revealed that among several clinical variables at the initial presentation of the patients, only the time of the last ejaculation (= little interval to the onset of scrotal symptoms) was significantly associated with the occurrence of hematospermia ($p < 0.001$, Table S1).

An infectious etiology of acute epididymitis was detectable in 198 of 274 patients (72%) without hematospermia and 28 of 50 patients (56%) with hematospermia. A total of 285 pathogens were found in 274 patients in the subgroup without hematospermia, with two pathogens in seven patients and three pathogens in two patients. In the subgroup with hematospermia, 54 pathogens were detected in 50 patients, with four patients having two different pathogens. It should be emphasized that the pathogen spectrum was comparable in both epididymis subgroups and that, in particular, the proportion of the two major pathogens *E. coli* (32% vs. 28%) and *C. trachomatis* (21% vs. 17%) did not differ significantly between the subgroups ($p = 0.859$, Table 2).

3.2 | Clinical data on hematospermia control group

In total, 56 patients with self-reported hematospermia without any symptoms or signs of acute epididymitis were recruited as a control group. The clinical data can be found in Table 3. It should be noted that only 11 patients (20%) presented to our clinic within 1 week of the onset of hematospermia. The median time of presentation after the onset of hematospermia was 157 days. With a median CRP value of 0.6 mg/l and a PSA value of 0.8 ng/ml, these patients had neither systemic inflammation nor relevant prostatitis. The etiology was predominantly idiopathic (52%), only two patients (4%) had a previously unknown prostate carcinoma. None of the patients developed acute epididymitis in the next 4 weeks after presentation.

3.3 | Clinical course

Of the 324 patients, a total of 178 patients (54%) were treated as inpatients. The median duration of hospitalization was five days (IQR:

TABLE 1 Clinical parameters of the epididymitis cohort patients.

	Acute epididymitis		
	No hematospermia ($n = 274$)	Hematospermia ($n = 50$)	*p*-Value
Patient demographics			
Age, yr, median (IQR)	43 (28–55)	39 (28–53)	0.401*
Side (right/left/bilateral), *n* (%)	139/127/8 (51/46/3)	31/17/2 (62/34/4)	0.268‡
Indwelling catheter, *n* (%)	0 (0)	1 (2)	0.154†
Fever > 38°C, *n* (%)	60 (22)	10 (20)	0.853†
Patient history			
Onset of symptoms, d, median (IQR)	2 (1–5)	3 (1–5)	0.717*
Pain severity score, 0-10, median (IQR)	7 (5–8)	7 (5–8)	0.829*
Last ejaculation, d, median (IQR)	7 (3–15)	4 (1–7)	<**0.001**†
Time from the last ejaculation to the onset of scrotal pain, d, median (IQR)	5 (0–14)	1 (−1–4)	<**0.001**†
Analgetic premedication, *n* (%)	103 (38)	19 (38)	1.000†
Antibiotic premedication, *n* (%)	80 (29)	21 (42)	0.096†
Urethritis, *n* (%)	8 (3)	1 (2)	1.000†
Dysuria, *n* (%)	80 (29)	11 (22)	0.392†
Endourological surgery within last 20 d, *n* (%)	1 (0.4)	0 (0)	1.000†
Respiratory tract symptoms within last 10 d, *n* (%)	13 (5)	0 (0)	0.232†
Sexually active with a partner within the last 6 months, *n* (%)	253 (93)	48 (96)	0.550†
Sexual history suggestive of STIs, *n* (%)	66 (24)	15 (30)	0.378†
History of previous epididymitis, *n* (%)	16 (6)	2 (4)	1.000†
Laboratory findings			
WBC, giga/l, median (IQR)	11.6 (9.3–15.8)	12.1 (9.3–16.0)	0.821*
CRP, mg/l, median (IQR)	34.2 (10.6–93.6)	32.5 (17.6–91.2)	0.668*
PSA, ng/ml, median (IQR)	1.8 (0.8–4.0)	3.1 (1.8–5.3)	**0.004***
Leukocytes, /μl urine, median (IQR)	250 (25–500)	500 (75–500)	0.072*
Local symptoms			
Scrotal wall induration, *n* (%)	38 (14)	6 (12)	0.826†
Epididymal pain on palpation, *n* (%)#	271 (99)	49 (98)	0.490†
Testicular pain on palpation, *n* (%)#	125 (46)	23 (46)	1.000†
Ultrasound parameters			
Transrectal ultrasound volume, ml, median (IQR)	19.4 (14.8–25.3)	18.8 (14.5–25.0)	0.387*
Testicular volume affected side (ml)§	17.1 (13.0–21.4)	15.9 (12.7–19.3)	0.169*
Testicular volume healthy side (ml)§	13.4 (11.0–16.8)	13.1 (11.6–17.5)	0.808*
Epididymal head thickness affected side (mm)§	9.8 (7.8–12.4)	9.0 (8.1–11.2)	0.368*
Epididymal head thickness healthy side (mm)§	8.5 (7.1–9.8)	8.0 (6.7–10.1)	0.580*
PSV testicular artery affected side (cm/sec)§	20.3 (15.5–25.4)	18.7 (14.7–23.2)	0.177*
PSV testicular artery healthy side (cm/sec)§	9.4 (7.4–11.9)	11.1 (8.4–15.4)	**0.012***
Epididymal abscess in ultrasound, *n* (%)	23 (8)	0 (0)	**0.033**†

WBC = white blood cell count; CRP = C-reactive protein; PSA = prostate-specific antigen. *Mann-Whitney U test. †Fisher's exact test. ‡Chi square test. #e.g. no pain in patients with impaired sensory function due to spinal cord injury. §only patients with unilateral disease.

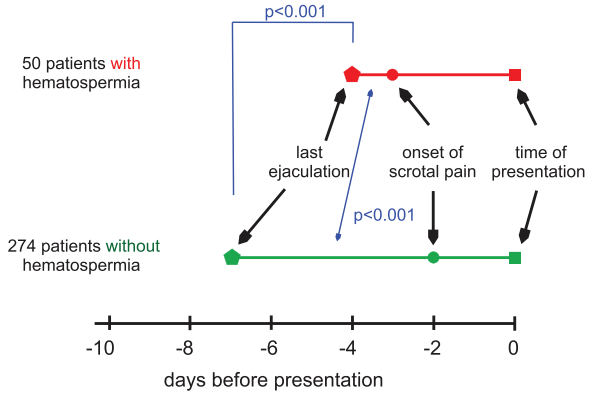

FIGURE 2 Graphical representation of the two time points "last ejaculation" and "onset of scrotal pain" in relation to the "time of presentation" in the emergency department. Significantly shorter intervals between "last ejaculation" and "time of presentation" or time period "last ejaculation" to "onset of scrotal pain" in the group of patients with acute epididymitis and self-reported hematospermia (for both $p < 0.001$, Mann-Whitney U test).

4–6). There was no difference between the two epididymitis subgroups in this regard (always $p > 0.05$). Conservative antibiotic therapy was successful in 98% of cases, only six patients (2%) required unilateral semicastration due to secondary testicular infarction (five patients in the group without hematospermia and one patient in the group with hematospermia, $p = 1$). Figure 3 shows the course of the PSA values over time. After 3 months, the PSA values in both epididymitis subgroups had normalized to 0.8 ng/ml (for both $p < 0.001$) and were thus comparable to those in the hematospermia control group (Figure 3, $p > 0.05$).

3.4 | Semen parameters in patients with and without hematospermia

To assess the impact of acute epididymitis on semen quality, patients were offered a semen analysis together with a measurement of sex hormones after the acute infection had resolved at day 14. In total, the analysis was performed on 126 patients without hematospermia and 31 with hematospermia. An overview of the two epididymitis subgroups as well as a comparison with the hematospermia control group can be found in Table 4. It should be emphasized that hematospermia could be objectified in 15 (12%) and 8 (26%) patients in the epididymitis group without and with self-reported hematospermia, respectively. All semen parameters and sex hormones between both subgroups of epididymitis patients were comparable (always $p > 0.05$) except for an increased number of seminal leukocytes in the hematospermia subgroup (2.8 million/ml vs. 1.0 million/ml, $p = 0.049$). When comparing the two epididymitis subgroups 14 days after initial presentation with the hematospermia control group, it is notable that the ejaculates of patients with epididymitis showed marked inflammation with increased pH, peroxidase-positive leukocyte counts, and elastase in combination with reduced levels of organ-specific markers

TABLE 2 Etiology of acute epididymitis*.

	No hematospermia ($n = 274$)	Hematospermia ($n = 50$)
Classical uropathogens		
Escherichia coli, *n (%)*	90 (32)	15 (28)
Haemophilus spp., *n (%)*	7 (3)	1 (2)
Enterococcus spp., *n (%)*	4 (1)	0 (0)
Pseudomonas spp. , *n (%)*	3 (1)	0 (0)
Klebsiella spp., *n (%)*	2 (1)	1 (2)
Lactobacillus spp., *n (%)*	2 (1)	0 (0)
Streptococcus spp., *n (%)*	2 (1)	0 (0)
Staphylococcus aureus, *n (%)*	1 (0.4)	1 (2)
Staphylococcus epidermidis, *n (%)*	1 (0.4)	0 (0)
Citrobacter spp., *n (%)*	1 (0.4)	0 (0)
Serratia marcescens, *n (%)*	1 (0.4)	0 (0)
Proteus spp., *n (%)*	1 (0.4)	0 (0)
Morganella spp., *n (%)*	1 (0.4)	0 (0)
Aerococcus spp., *n (%)*	1 (0.4)	0 (0)
Proprionibacterium spp., *n (%)*	1 (0.4)	0 (0)
Eubacterium spp., *n (%)*	1 (0.4)	0 (0)
STI-PCR in all sexually active patients		
Chlamydia trachomatis, *n (%)*	61 (21)	9 (17)
Neisseria gonorrhoeae, *n (%)*	8 (3)	0 (0)
Mycoplasma spp., *n (%)*	8 (3)	4 (7)
Ureaplasma spp., *n (%)*	10 (4)	1 (2)
Trichomonas vaginalis, *n (%)*	1 (0.4)	0 (0)
Viral analysis in patients without bacterial pathogen		
Enterovirus, *n (%)*	2 (1)	0 (0)
No pathogen		
No pathogen identified, *n (%)*	76 (28)	22 (44)

*No significant differences between the pathogen spectra of both epididymitis subgroups ($p = 0.859$; Chi-square test).

(zinc, alpha-glucosidase) and a reduced sperm concentration (all cases $p < 0.01$).

When comparing the ejaculates of epididymitis patients at day 14 who had hematospermia and those who did not in this ejaculate analysis, then it appears that hematospermia is associated with approximately 10-fold increased levels of peroxidase-positive leukocytes and elastase (Figure 4A,B, for both $p < 0.001$), while all other semen parameters were not significantly different. A similar trend was seen in patients in the hematospermia control group, with hematospermia being present in only 19 of the 36 patients undergoing semen analysis (Figure 4C and Figure 4D, for both $p > 0.05$).

TABLE 3 Clinical data of patients with isolated hematospermia (control group).*

Parameter	Hematospermia cohort ($n = 56$)
Patient characteristics	
Age, yr, median (IQR)	44 (33–57)
Time period first hematospermia episode to the first presentation, d, median (IQR)	157 (13–494)
Prevalent at vaginal intercourse/masturbation/both, *n (%)*	23/23/10 (41/41/18)
Number of previous bloody ejaculations	8 (2-48)
Color of hematospermia (light red vs. rusty brown vs. both), *n (%)*	22/25/9 (39/45/16)
Urethritis, *n* (%)	1 (2)
Dysuria, *n* (%)	12 (21)
Previously known diseases of the prostate, *n (%)*	3 (5)
Endourological surgery within last 20 d, *n* (%)	2 (4)
Ongoing therapy with anticoagulants, *n (%)*	7 (13)
Unprotected intercourse with new partners last 3 months, *n (%)*	6 (11)
History of vasectomy, *n (%)*	3 (5)
History of hypertension, n (%)	11 (20)
History of STIs last 10 years, *n (%)*	3 (5)
CRP, mg/l, median (IQR)	0.6 (0.5–1.2)
PSA, ng/ml, median (IQR)	0.8 (0.6–1.2)
Transrectal ultrasound volume, ml, median (IQR)	21.8 (16.7–29.9)
Presumed etiology	
Idiopathic	29 (52)
Congenital malformations	0 (0)
Inflammation/infections	17 (30)
Obstruction	5 (9)
Malignancies	2 (4)
Vascular abnormalities	0 (0)
Iatrogenic/trauma	0 (0)
Systemic causes	3 (5)

*without any symptoms or signs of acute epididymitis.

4 | DISCUSSION

In a large prospective study of 324 patients with acute epididymitis, we demonstrated for the first time that self-reported hematospermia was present in a median of 24 h before the onset of scrotal symptoms in 15% of patients. On the other hand, none of the 56 patients from a control group suffering from hematospermia unrelated to acute epididymitis developed any symptoms or signs of epididymitis within the next 4 weeks after initial presentation.

It is repeatedly reported that hematospermia causes fear in many men, especially of having a malignancy in the genitourinary tract.[1] However, none of the 50 patients with hematospermia and epididymitis presented themselves solely because of hematospermia. All patients first came to us because of scrotal swelling and pain. Among the patients of the hematospermia control group who presented to the emergency department, only 20% of the men had the event of hematospermia within the previous week. Thus, hematospermia does seem to cause less anxiety among those affected than generally thought.

Several underlying reasons for hematospermia have been acknowledged and can be classified into various categories.[5] Nevertheless, in about half of the cases the etiology remains unknown. In a meta-analysis of 20 studies, 603/1163 (52%) of cases were unexplained.[4] This corresponds exactly to the data of our study, where 52% of the cases in the hematospermia control group could not be assigned to an etiology. The reason for the high rate of idiopathic cases could be that only a few patients present early (e.g., within a week) and thus not in the acute phase, so infections, in particular, may not be detected after many months. This delay could explain why in a tertiary referral center an unexplained etiology was reported in as many as 82% of the 300 patients studied.[21]

There is consensus that etiologically infections and inflammation comprise the largest group of cases in patients with hematospermia. Thus, in a study of 300 patients, 10% of cases in men < 40 years of age and 15% of cases in men > 40 years of age could be attributed to lower urinary tract infections.[21] However, the examinations carried out (e.g. clinical work-up, urine, ejaculate, STI screening) in the highly heterogeneous studies differed widely. In a meta-analysis of eight studies with 836 patients, a total of 20% of the cases were attributed to an inflammatory cause.[4] In our study, 30% of patients had an infectious/inflammatory cause. This higher prevalence may be due to the fact that we asked all patients to provide a semen sample and also screened for classical uropathogens and STIs in all urine and semen samples. This approach was not systematically performed in other studies contributing to the above-mentioned meta-analysis.[4]

It would be interesting to reveal from which organ the hematospermia results. We know that various changes in the prostate and seminal vesicles (prostatitis, prostatic cysts, vesiculitis, and ejaculatory duct obstruction) can cause hematospermia.[4,22,23] Since the epididymis is the endpoint in the ascending infection, but hematospermia occurs one day before scrotal symptoms, the reason for hematospermia must be more distal in the genitourinary tract (e.g. prostate, seminal vesicles). This hypothesis is supported by the significantly elevated PSA levels as a sign of concomitant prostatitis in epididymitis patients with hematospermia compared to those without hematospermia. Additionally, a more comprehensive sonography of the prostate with the determination of perfusion parameters in the organ (e.g., arterial peak systolic velocity) could have been helpful to substantiate prostatitis.[24–27] Unfortunately, these examinations were not performed, which is a limitation of the study.

To the best of our knowledge, our study is the first to show that the two major pathogens of acute epididymitis, namely *E. coli* and *C. trachomatis*[9] can both cause hematospermia with equal frequency. This is surprising because uropathogenic *E. coli*, having multiple virulence factors actively present, are associated with an unfavorable outcome of epididymitis when compared to *C. trachomatis* infections.[28]

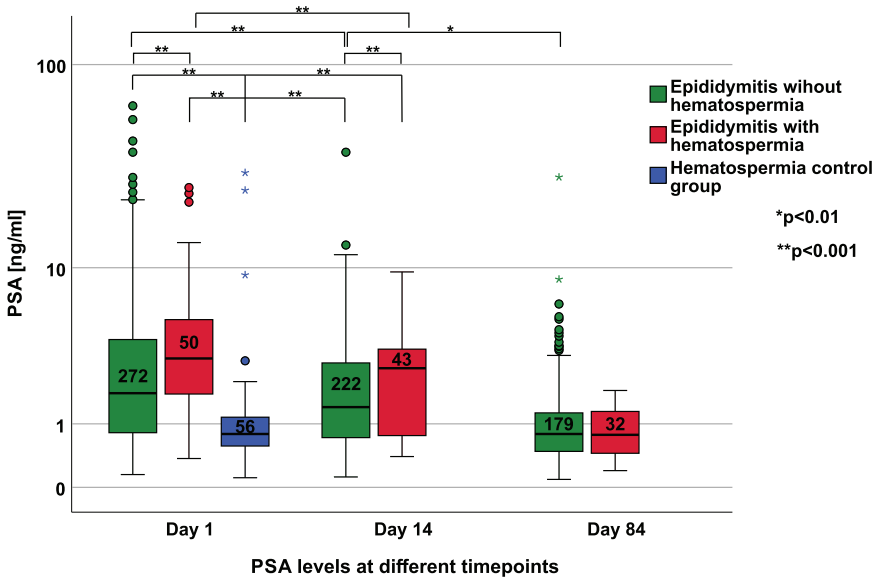

FIGURE 3 Development of prostate-specific antigen (PSA) levels over time in epididymitis patients with and without hematospermia in comparison with the isolated hematospermia control group. Box and whisker plots display median values, quartiles, outliers (o/*), and the number of patients. Epididymitis patients with hematospermia had higher PSA levels than epididymitis patients without hematospermia on days 1 and 14 (each $p < 0.001$, Mann-Whitney U test). During the course of the study, the initially elevated PSA levels normalized in both epididymitis groups ($p < 0.001$, Wilcoxon test). Thus, at day 84, the PSA values of the epididymitis groups no longer differed from those of the hematospermia control group ($p < 0.001$ each, Mann-Whitney U test).

TABLE 4 Semen parameters and sex hormones comparing epididymitis patients without and with hematospermia to the hematospermia control group.

Parameter	Acute epididymitis		Isolated hematospermia cohort	*p*-Value
	no hematospermia ($n = 126$)	hematospermia ($n = 31$)	($n = 36$)	
Semen				
Days first presentation to semen analysis, d, median (IQR)	12 (5–16)	9 (3–15)		0.165*
Hematospermia, n (%)	15 (12)	8 (26)	19 (53%)	<0.001†
Volume (ml), median (IQR)	1.9 (1.0–3.0)	2.0 (1.5–4.2)	1.5 (1.2–2.7)	0.217‡
pH value, median (IQR)	8.0 (7.6–8.6)	8.0 (7.8–8.6)	7.5 (7.2–7.9)	<0.001‡
Sperm concentration (million/ml), median (IQR)	12.5 (2.7–32.5)	9.2 (0.5–28.7)	30.4 (7.8–107.7)	<0.007‡
Progressive sperm motility (%), median (IQR)	42 (26–54)	53 (27–62)	36 (6–53)	0.035‡
Normal sperm morphology (%), median (IQR)	5 (2–10)	7 (0–13)	7 (2–13)	0.645‡
Zinc (μmol/ejaculate)[b], median (IQR)	3.9 (1.0–7.6)	2.3 (0.6–3.8)	16.1 (2.6–40.0)	<0.001‡
Fructose (μmol/ejaculate), median (IQR)	10.5 (5.2–21.3)	11.3 (4.8–24.2)	11.3 (1.7–45.1)	0.983‡
Glucosidase (mU/ejaculate), median (IQR)	18.5 (10.0–36.4)	25.3 (14.4–58.1)	66.5 (30.8–178.4)	<0.001‡
Peroxidase- positive Leukocytes (million/ml), median (IQR)	1.0 (0.3–4.7)	2.7 (0.7–8.0)	0.3 (0.2–1.5)	0.001‡
Elastase (ng/ml)[a], median (IQR)	657 (299–2000)	1138 (224–2000)	98 (31–316)	<0.001‡
Hormones				
FSH (mU/ml), median (IQR)	4.1 (2.9–6.9)	4.8 (3.5–5.9)	4.4 (2.5–5.9)	0.822‡
LH (mU/ml), median (IQR)	4.6 (3.3–6.7)	4.3 (3.4–6.1)	2.8 (2.2–3.7)	<0.000‡
Testosterone (nmol/l), median (IQR)	15.3 (11.1–19.4)	16.6 (11.2–20.6)	16.1 (13.1–19.3)	0.575‡
Free testosterone (pmol/l), median (IQR)	290.8 (231.0–371.0)	282.1 (243.9–374.8)	282.6 (226.6–327.5)	0.775‡
SHBG (nmol/l), median (IQR)	35.8 (24.8–48.8)	35.5 (28.3–44.3)	43.7 (28–51.4)	0.423‡
Albumin (g/l), median (IQR)	45.2 (43.2–46.4)	45.3 (43.8–46.5)	46.6 (44.0–48.0)	0.144‡
Estradiol (pmol/l), median (IQR)	121.1 (95.4–145.0)	117.5 (91.8–182.8)	123.0 (90.6–137.7)	0.719‡
Prolactin (uIU/ml), median (IQR)	192 (149–263)	188 (156–264)	122 (80–143)	<0.001‡

*Mann-Whitney U test. †Chi square test. ‡Kruskal-Wallis test.

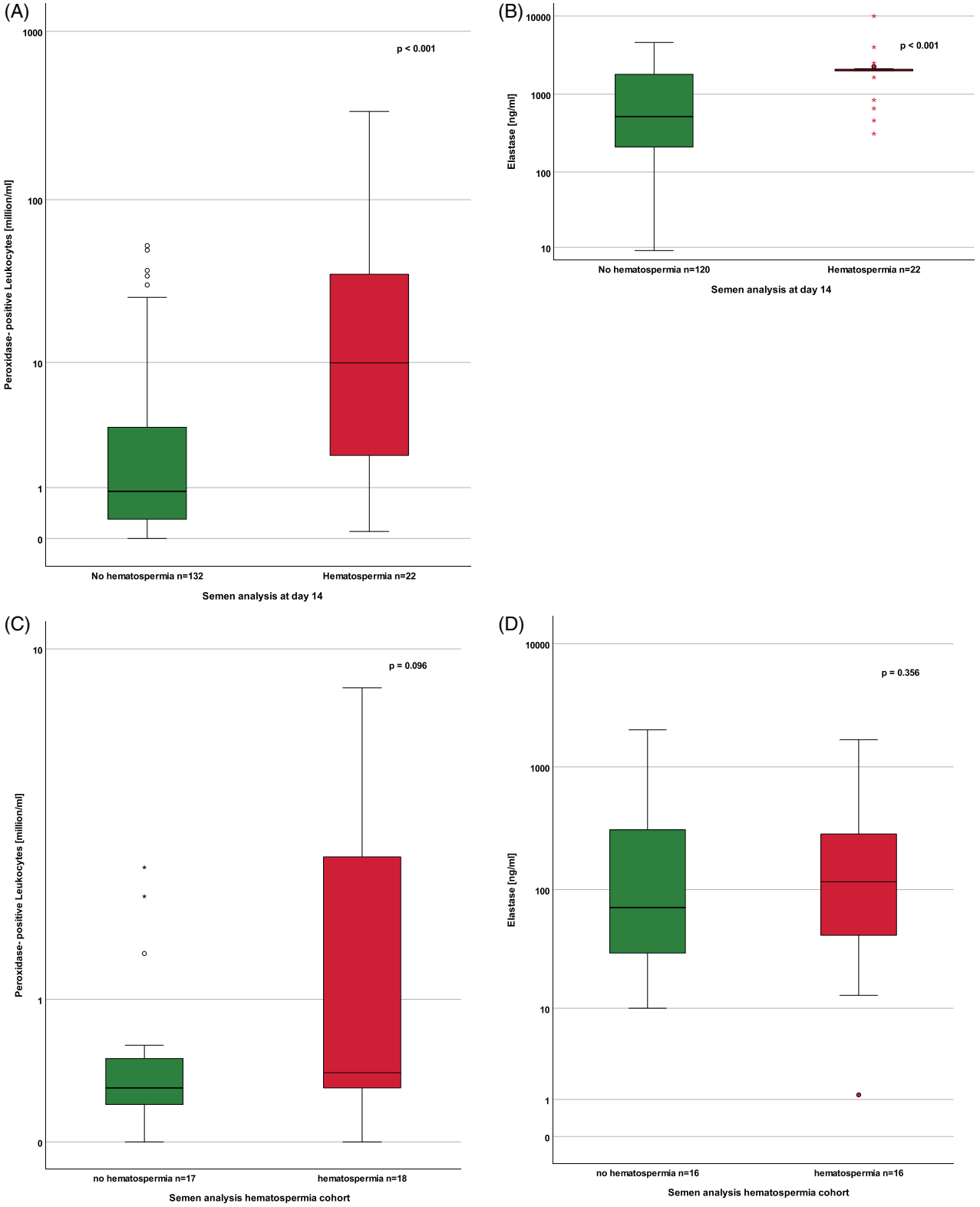

FIGURE 4 Association between markers of inflammation and hematospermia objectified in semen analysis. (A) Comparison of peroxidase-positive leukocytes in ejaculates of epididymitis patients with and without hematospermia at 14 days after acute infection. $p < 0.001$, Mann-Whitney U test. (B) Comparison of elastase in ejaculates of epididymitis patients with and without hematospermia at 14 days after acute infection. $p < 0.001$, Mann-Whitney U test. (C) Comparison of peroxidase-positive leukocytes in ejaculates of patients from the hematospermia group showing a trend towards inflammation in hematospermia. $p = 0.096$, Mann-Whitney U test. (D) Comparison of elastase levels in ejaculates of patients from the hematospermia group showing a trend towards inflammation in hematospermia. $p = 0.356$, Mann-Whitney U test. Box and whisker plots display median values, quartiles, and outliers (o/*).

In addition, although *E. coli* may be etiologic in epididymitis in both young and old patients, sexually active men are naturally more likely to have *C. trachomatis* as the causative pathogen than older men and the disease symptoms are usually clinically milder.[9] The observation that chlamydia can cause hematospermia has only been described in a few individual cases. For example, a study using systematic STI screening in patients with hematospermia, where non-infectious causes had already been ruled out, detected *C. trachomatis* in 4 of 16 patients and *U. urealyticum* in another patient. Interestingly, the hematospermia resolved after antibiotic therapy, which suggests infection as an etiologic cause for hematospermia.[29] In another study of 1236 patients who underwent cystoscopy, there were 10 patients with bullous changes in the prostatic urethra. After comprehensive (molecular) microbiological diagnostics, all of them could be proven to have been infected by *C. trachomatis*. One of these patients reported hematospermia beforehand, which is why he underwent cystoscopic clarification.[30] Interestingly, in addition to *C. trachomatis* and *U. urealyticum*, *Trichomonas vaginalis* can also cause hematospermia.[31]

There have been no comprehensive studies evaluating semen parameters in patients with and without hematospermia. We could show in a large number of patients that hematospermia is associated with leukocytospermia and increased levels of seminal neutrophil elastase in patients with epididymitis. Here, almost 10-fold increases were seen in both parameters. Interestingly, all other semen parameters (sperm parameters and biochemical markers) were not significantly different between the epididymitis subgroups. In the hematospermia control group, the same tendency was seen, but the differences were not significant between the patients who then had hematospermia and those who did not have hematospermia objectified by the semen analysis.

Although acute epididymitis typically occurs unilaterally, adverse effects on fertility are feared. However, few studies have examined semen quality after acute epididymitis. A systematic analysis of 5 studies with a total of 211 patients found that approximately 40% of patients had persistent impaired semen quality.[10] Since antibiotic therapy is primarily recommended for acute epididymitis, it must be discussed whether antibiotic therapy impairs semen quality or whether the infection is the primary source. Unfortunately, very few studies on the effects of antibiotic therapy on sperm parameters in humans are available, while a wide variety of potentially negative effects on sperm parameters and testicular tissue have been documented in animal models.[32] Two studies exist that did not use antibiotic therapy in acute epididymitis due to the lack of knowledge about *C. trachomatis* have reported a severe impairment of sperm concentration.[33,34] In addition, there is an excellent study of 37 patients with acute epididymitis in which improvement in sperm parameters was achieved by antibiotic therapy of acute epididymitis with ofloxacin for 10–14 days.[35] Thus, the negative effects of infection—and not antibiotic therapy—seem to be of major relevance in acute epididymitis for impairment of semen quality.

5 | CONCLUSIONS

We demonstrated for the first time in a large prospective study that in 15% of sexually active patients, hematospermia may be a harbinger of acute epididymitis, occurring just one day before the onset of scrotal pain, and both *E. coli* and *C. trachomatis* may cause hematospermia with equal frequency. Therefore, in patients presenting as an emergency with hematospermia, a comprehensive clinical and sonographic evaluation should be performed regarding the presence of a seminal tract infection to potentially avoid epididymitis that may develop in the next few days.

AUTHOR CONTRIBUTIONS

Florian Dittmar: Formal analysis, Investigation, Data Curation, and Writing—Original Draft. Jens Rosellen: Investigation and Writing—Review & Editing. Leo Reiser: Investigation and Writing—Review & Editing. Moritz Fritzenwanker: Investigation, Resources, Data Curation, and Writing—Review & Editing. Arne Hauptmann: Investigation and Writing—Review & Editing. Thorsten Diemer: Investigation and Writing—Review & Editing. Hans-Christian Schuppe: Conceptualization, Investigation, Data Curation and Writing—Original Draft. Florian Wagenlehner: Conceptualization, Writing—Review & Editing and Supervision. Adrian Pilatz: Conceptualization, Formal analysis, Investigation, Data Curation, Writing—Original Draft, Visualization, Project administration, and Funding acquisition.

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CONFLICT OF INTEREST STATEMENT

Thorsten Diemer has the following disclosures: Lilly Deutschland (Shareholdings, Employment family member), AMS/Boston Scientific (Lecture honoraria), Cheplapharm Arzneimittel GmbH (Consulting), Advance Medical S.A. (Consulting), Teladoc Health (Consulting), Marpinion GmbH (Consulting), Ferring Arzneimittel GmbH (Lecture honoraria), Janssen-Cilag GmbH (Lecture honoraria), MedUpdate GmbH (Lecture honoraria). All other authors have no conflict of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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