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European Association of Urology

Platinum Priority – Infections

Editorial by Jean-Nicolas Cornu and Franck Bruyère on pp. 436–437 of this issue

Acute Epididymitis Revisited: Impact of Molecular Diagnostics on Etiology and Contemporary Guideline Recommendations

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Article info

Article history:
Accepted December 3, 2014

Keywords:
Antimicrobial therapy
Epididymitis
Guideline recommendations
Sexually transmitted infections

Abstract

Background: Acute epididymitis is a common infectious disease of unknown etiology in about 30% of cases with guidelines based on studies published >15 yr ago.
Objective: To investigate the etiology of acute epididymitis using state-of-the-art methods and to provide rational data for antimicrobial therapy and clinical management.
Design, setting, and participants: Between 2007 and 2013, 237 patients (150 antimicrobially naive and 87 antibiotically pretreated) with acute epididymitis underwent comprehensive investigation comprising microbiologic cultures, polymerase chain reaction (PCR) for sexually transmitted infections (STIs), 16S ribosomal DNA (rDNA) analysis, and PCR detection of 23 viruses. Clinical management followed international guidelines.
Outcome measures and statistical analysis: Etiology, clinical management, and outcome after 3 mo were assessed.
Results and limitations: A causative pathogen, predominantly *Escherichia coli* (56%), was identified in 132 antibiotic-naive patients (88%) and 44 pretreated patients (51%); 16S rDNA analysis increased the detection rate by 10%. STIs were present in 34 cases (14%) (25 patients with *Chlamydia trachomatis*) and were not restricted to a specific age group. Enteroviruses were found in only two patients (1%). In naive patients, cultured bacteria were susceptible to fluoroquinolones and group 3 cephalosporins in >85% of cases (preateted patients: 42% and 67%, respectively). Primary empirical therapy was continued in 88% of naive patients for 11 d and in 77% of pretreated patients for 13 d with indwelling urinary catheters, rendering patients as high risk for switching. Only six patients (2.5%) underwent semicastration. Prostate-specific antigen levels halved within 3 mo, except in patients who were antibiotic naive and without detected pathogens. Study limitations included a lack of susceptibility testing in cases of STIs.
Conclusions: Even in antimicrobially pretreated patients, acute epididymitis is mainly of bacterial origin. STIs are not limited to patients aged <35 yr. Viral epididymitis seems a rare condition. Current guideline recommendations on empirical antimicrobial therapy are adequate.
Patient summary: Patients with acute epididymitis should receive appropriate diagnostics and antimicrobial therapy for safe conservative management.

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http://dx.doi.org/10.1016/j.eururo.2014.12.005
0302-2838/

1. Introduction

Acute epididymitis is a common condition with recent epidemiological data from the United Kingdom reporting incidence rates of about 25 of 10 000 person-years [1]. The clinical spectrum ranges from mild epididymal tenderness to severe systemic disease [2]. Despite the existence of pertinent guidelines [3,4], up to 50% of patients receive inadequate diagnostics and therapy [5,6].

In 1927, Campbell considered epididymitis to be a result of pathogen ascension through the urogenital tract [7]. This hypothesis was confirmed by studies investigating pathogens isolated simultaneously from the urine/urethra and epididymis [8–10]. Another diagnostic breakthrough followed with the discovery that *Chlamydia trachomatis* was responsible for up to 70% of cases with so-called idiopathic epididymitis [11]. Over the past 10 yr, advances in molecular diagnostic methods have opened up new perspectives in microbial identification and characterization [12]. However, such possibilities have scarcely been considered in investigating the etiology of viral and idiopathic epididymitis [2,8,13–16].

Medical and microbiologic diagnostics with accurate identification of infectious agents are important for adequate patient management with regard to short-term and long-term sequelae [2,5,17–20]. Several of the pioneer studies investigating sexually transmitted infections (STIs) as a putative cause for acute epididymitis reported on a limited number of patients who were mainly derived from army hospitals or specialized STI centers [10,11,21]. All this has resulted in a general consensus that epididymitis in men aged <35 yr is most likely caused by STIs and in men aged >35 yr by enteric pathogens [3].

Similarly, current guideline recommendations from the European Association of Urology (EAU)/Centers for Disease Control and Prevention (CDC) on antimicrobial therapy depend on only a few studies that were published >15 yr ago [2,10,13,21,22]. Thus the impact of increasing rates of antibiotic resistance during the last few years is unknown [14,15]. Guidelines currently recommend ceftriaxone plus doxycycline for men at risk for STIs and (lev)ofloxacin for those with epididymitis most likely caused by enteric pathogens, and a combination of a fluoroquinolone and ceftriaxone for those at risk for both STIs and enteric pathogens [3,4].

The aim of this prospective study was to investigate the etiology of acute epididymitis by applying state-of-the-art microbiologic and molecular methods for identification of bacterial and viral pathogens and to relate this to antimicrobial therapy and clinical management in patients with and without previous antibiotic treatment.

2. Materials and methods

2.1. Study population

After receiving approval from the institutional review board (reference no. 100/7), we conducted a prospective study on the etiology of acute epididymitis at the Department of Urology, Pediatric Urology and Andrology, Giessen, Germany (German clinical trials registration DRKS00003325) from July 2007 to December 2013. The inclusion criterion was acute epididymitis, defined as onset within the last 2 wk, enlarged epididymis on palpation typically associated with pain, and epididymal hyperemia on ultrasound [3,4]. A total of 251 consecutive patients with acute epididymitis without evidence for other primary scrotal diseases (eg, torsion or tumor) were screened. Exclusion criteria were missing written informed consent, no urine samples stored at −80 °C, or age <18 yr. Altogether 237 patients were enrolled (Supplementary Fig. 1). The patients with acute epididymitis presented initially at the emergency department without the need for a medical referral. They were categorized into two groups: antimicrobially naive and pretreated with antibiotic therapy requesting a second opinion. At the same time, a comprehensive medical history was obtained, and patients were surveyed for previous external antimicrobial therapy (Supplementary Table 1).

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 orally and recorded in degrees centigrade. In addition, scrotal contents were evaluated by ultrasound, as described [18].

2.3. Laboratory methods

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

2.4. Bacteriologic diagnostics

A standardized and extensive microbiological work-up was performed (see the Supplement and Supplementary Fig. 2 for details). Patients who were sexually active within the last 12 mo (n = 137) were screened for STIs in the urethra, targeting *Mycoplasma genitalium*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, *Chlamydia trachomatis*, and *Neisseria gonorrhoeae* by means of polymerase chain reaction (PCR). All patients without an indwelling urinary catheter were also asked to provide midstream urine. To prevent contamination in patients with indwelling catheters, the existing catheter was replaced and a urine specimen sampled afterward. All urine specimens were inoculated on agar plates and identified. They subsequently underwent antimicrobial susceptibility testing. Negative urine cultures were subjected to 16S ribosomal DNA (rDNA) analysis, as described [23].

2.5. Virologic diagnostics

Viral investigations were performed on 23 different viruses as real-time assays in all patients without detected bacterial pathogens (n = 63) in cryopreserved samples (see Supplement for details).

2.6. Therapy and follow-up

Patients were managed on an outpatient basis or hospitalized in cases with complicating factors as medically indicated (Supplementary Fig. 3) [3,4]. In accordance with EAU/CDC guidelines, empirical therapy was initiated with levofloxacin 500 mg per day orally for 10 d in both groups. Hospitalized patients also received cefotaxime 2 g three times daily intravenously [3]. Exceptions included patients with allergies, contraindications, or previous susceptibility testing. If necessary, the dose was

Table 1 – Baseline characteristics

	Naive $n = 150$	Pretreated $n = 87$	p value
Patient demographics			
Age, yr, median (IQR)	52 (33–64)	56 (41–71)	0.094[*]
Side, right/left/bilateral, n (%)	72/70/8 (48/47/5)	43/40/4 (49/46/5)	0.957[**]
Indwelling catheter, n (%)	13 (9)	15 (17)	0.060[†]
Fever >38 °C, n (%)	46 (31)	18 (21)	0.129[†]
Patient history			
Onset of symptoms, d, median (IQR)	2 (1–3)	3 (1–5)	0.150[*]
Pain severity score, 0–10, median (IQR)	7 (4–8)	7 (4–8)	0.832[*]
Analgesic premedication, n (%)	44 (29)	28 (32)	0.662[†]
Urethritis, n (%)	1 (1)	5 (6)	0.026[†]
Dysuria, n (%)	40 (27)	29 (33)	0.301[†]
Endourolocal surgery within last 20 d, n (%)	4 (3)	1 (1)	0.655[†]
Respiratory tract symptoms within last 10 d, n (%)	8 (5)	5 (6)	1.000[†]
Sexually active within last 6 mo, n (%)	89 (59)	48 (55)	0.586[†]
Sexual history suggestive of STIs, n (%)	19 (13)	8 (9)	0.526[†]
History of previous epididymitis, n (%)	3 (2)	3 (3)	0.672[†]
Laboratory findings			
WBC, giga/l, median (IQR)	12.5 (9.7–16.0)	11.9 (9.8–17.6)	0.744[*]
CRP, mg/l, median (IQR)	52.2 (16.8–100.6)	63.1 (22.5–127.0)	0.215[*]
PSA, ng/ml, median (IQR)	2.1 (0.9–4.3)	2.0 (0.8–5.6)	0.797[*]
Leukocytes/μl urine, median (IQR)	500 (25–500)	100 (25–500)	0.045[*]
Prostate palpation			
Unsuspicious	130 (87)	78 (90)	0.279[**]
Not possible[§]	6 (4)	0 (0)	
Indurated	2 (1)	2 (2)	
Denied	12 (8)	7 (8)	
Prostate ultrasound			
Abscess formation	0 (0)	0 (0)	1.000[†]
Transrectal ultrasound volume, ml, median (IQR)	20.4 (14.9–27.9)	20.0 (15.9–29.7)	0.782[*]
Local symptoms			
Scrotal wall induration, n (%)	27 (18)	18 (21)	0.611[†]
Epididymal pain on palpation, n (%)[#]	149 (99)	83 (95)	0.062[†]
Testicular pain on palpation, n (%)	78 (52)	51 (59)	0.346[†]
Epididymal abscess on ultrasound, n (%)	9 (6)	7 (8)	0.596[†]

CRP = C-reactive protein; IQR = interquartile range; PSA = prostate-specific antigen; STI = sexually transmitted infection; WBC = white blood cell count.
[*] Mann-Whitney U test.
[**] Chi-square test.
[†] Fisher exact test.
[§] For example, rectum extirpation.
[#] For example, no pain in patients with impaired sensory function due to spinal cord injury.

adapted according to renal function ($n = 14$ cases). The primary antimicrobial regime was always switched in cases of antimicrobial resistance detected by susceptibility testing, persistent disease, and drug intolerance. Analgesic therapy (eg, diclofenac 75 mg twice daily) was offered to all patients. Duration of hospitalization and antibiotic and analgesic therapy as well as indications for surgery were documented.

After initial management, an early follow-up was scheduled after 10 d to assess the immediate response and a late follow-up after 3 mo to assess microbiologic cure and clinical outcome. Patients without a face-to-face late follow-up ($n = 59$) were interviewed by telephone to exclude treatment failure.

2.7. Statistical analysis

The demographics and characteristics of antibiotic-naive and pretreated patients were compared using the Mann-Whitney U test, Fisher exact test, or chi-square test, as indicated. Variables were expressed accordingly as medians and interquartile range (IQR) or number and percentage. Multivariate binary logistic regression analysis was performed to identify risk factors for treatment failure. A value of $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS v.22 for Windows (IBM GmbH, Ehningen, Germany).

3. Results

3.1. Study population

A total of 150 patients (63%) were antibiotic naive, and 87 (37%) had received antimicrobial treatment before admission (Table 1). Baseline characteristics were statistically balanced, except for lower levels of leukocyturia and higher frequency of urethritis in pretreated patients (all $p < 0.05$). Severe epididymitis as indicated by scrotal wall induration and epididymal abscess formation was present in 45 cases (19%) and 16 cases (7%), respectively. A subgroup analysis of patients with indwelling urinary catheters is provided in Supplementary Table 2.

3.2. Bacteriologic findings

By means of urine cultures and PCR techniques, a bacterial pathogen could be detected in 130 of 150 naive patients (87%) and 44 of 87 patients pretreated with antibiotics

Table 2 – Pathogen spectrum

	Naive	Pretreated
Bacterial culture in all patients	*n* = 150	*n* = 87
Escherichia coli, *n*	79	11
Enterococcus spp, *n*	6	4
Pseudomonas spp, *n*	6	4
Klebsiella spp, *n*	4	1
Staphylococcus aureus, *n*	2	1
Citrobacter spp, *n*	2	0
Serratia marcescens, *n*	2	0
Proteus spp, *n*	1	1
Morganella spp, *n*	1	0
Staphylococcus epidermidis, *n*	0	2
Patients with positive culture, *n*	96	21*
STI-PCR in all sexually active patients	*n* = 89	*n* = 48
Chlamydia trachomatis, *n*	20	5
Mycoplasma spp, *n*	7	1
Neisseria gonorrhoeae, *n*	2	4
Sexually active patients with positive STI, *n*	28	9†
Patients with negative culture and negative STI-PCR, *n*	29	57
16S rDNA analysis in culture- and STI-negative patients	*n* = 29	*n* = 57
Escherichia coli, *n*	0	8
Proteus spp, *n*	0	2
Staphylococcus epidermidis, *n*	0	1
Aerococcus spp, *n*	0	1
Propionibacterium spp, *n*	0	1
Haemophilus spp, *n*	5	1
Lactobacillus spp, *n*	2	0
Bacteroides spp, *n*	1	0
Eubacterium spp, *n*	1	0
Patients with positive 16S rDNA analysis, *n*	9	14‡
Viral analysis in patients without bacterial pathogen	*n* = 20	*n* = 43
Enterovirus, *n*	2	0

PCR = polymerase chain reaction; rDNA = ribosomal DNA; STI = sexually transmitted infection.
* $p < 0.001$ vs naive; Fisher exact test.
† $p = 0.157$ vs naive; Fisher exact test.
‡ $p = 0.609$ vs naive; Fisher exact test.

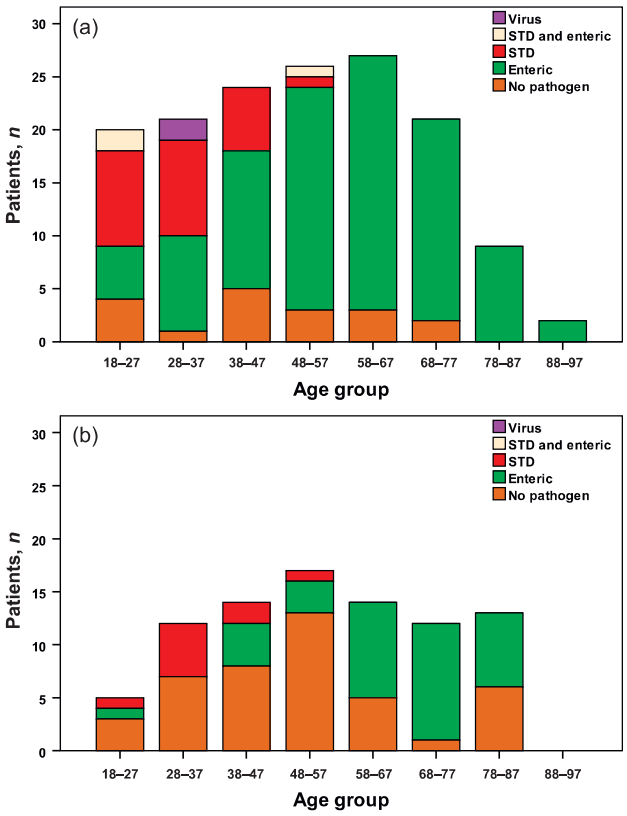

Fig. 1 – Pathogen distribution according to patient age (a) in 150 antibiotic-naive patients and (b) in 87 pretreated patients. STD = sexually transmitted disease.

(51%) (Table 2). *Escherichia coli* was the predominant etiologic pathogen in 98 cases (56%). Results of 16S rDNA analysis showed different pathogen spectra in naive compared with pretreated patients (Table 2).

Although sexual history suggested STIs in 27 patients, STI pathogens were detected in only 17; in another 18 cases with documented STIs, the sexual history was unrewarding ($p < 0.001$; Fisher exact test). STIs were more common in younger patients, without a strict age limit (median age: 34 yr; IQR: 24–41; Fig. 1). In patients aged <35 yr, STIs were detected in 21 of 50 cases (42%); common urinary tract pathogens were considered etiologically relevant in 14 of 50 cases (28%), and 3 of 50 cases (6%) experienced both STIs and enteric pathogens. Finally, patients with indwelling urinary catheters were found to harbor a wide spectrum of different bacteria (Supplementary Table 3).

Susceptibility to common antibacterial agents was assessed in 103 pathogens isolated from 96 naive patients and 24 pathogens from 21 pretreated patients. Overall, >85% of pathogens were susceptible to third-generation cephalosporins, fluoroquinolones, and aminoglycosides, with greatly reduced susceptibility rates in pretreated patients and those with indwelling urinary catheters (Fig. 2).

3.3. *Virologic findings*

Enteroviruses were detected in just 2 of 20 naive patients, but they were nevertheless deemed etiologically relevant because they were present in the acute phase and absent in the late follow-up investigation after 3 mo. Neither the mumps virus nor any other respiratory viruses were detected at any time. The BK virus was retrieved from 9 of 63 urine samples (14%) at first presentation and typically again at late follow-up; the presence of Epstein-Barr virus was related to leukocytes (Supplementary Table 4, Supplementary Fig. 4).

3.4. *Antimicrobial therapy and patient management*

Primary antibiotic treatment remained unaltered in 132 of 150 naive patients (88%) and 67 of 87 pretreated patients (77%) ($p = 0.042$; Fisher exact test). Reasons for therapy alterations included resistant strains ($n = 15$), persistent disease ($n = 11$), or others ($n = 12$) (Table 3). Multivariate regression analysis identified indwelling catheters, testicular pain, and CRP levels as independent risk factors for treatment failure ($n = 29$; resistant strains, persistent disease, semicastration) (Supplementary Table 5).

Table 3 – Therapy-related parameters of antibiotic-naive and pretreated patients

	Naive $n = 150$	Pretreated $n = 87$	p value
Primary empirical antimicrobial therapy			
Fluoroquinolone^ only, *n* (%)	67 (45)	30 (34)	
Fluoroquinolone^ plus cephalosporin group 3, *n* (%)	64 (43)	37 (43)	
Fluoroquinolone^ plus other antibiotic class, *n* (%)	8 (5)	3 (3)	0.140‡
Cephalosporin group 3 only, *n* (%)	6 (4)	10 (11)	
Cephalosporin group 3 plus other antibiotic class, *n* (%)	1 (1)	1 (1)	
Other antibiotic class only, *n* (%)	4 (3)	6 (7)	
Change of empirical antimicrobial therapy			
No change, *n* (%)	132 (88)	67 (77)	0.042†
Resistant strain, *n* (%)	7 (5)	8 (9)	
Persistent disease, *n* (%)	4 (3)	7 (8)	
Other factors (intolerance, allergy), *n* (%)	7 (5)	5 (6)	
Overall antimicrobial therapy			
Patients with one antimicrobial class, *n* (%)	61 (41)	31 (36)	
Patients with two antimicrobial classes, *n* (%)	76 (51)	39 (45)	0.118*
Patients with three antimicrobial classes, *n* (%)	11 (7)	14 (16)	
Patients with four antimicrobial classes, *n* (%)	2 (1)	3 (3)	
Duration of antimicrobial therapy, d, median (IQR)	11 (8–15)	13 (10–16)	0.073*
Analgesic therapy			
None, *n* (%)	24 (16)	16 (18)	0.676‡
Patients with diclofenac, *n* (%)	116 (77)	62 (71)	
Patients with other therapy, *n* (%)	10 (7)	9 (10)	
Analgesic therapy, d, median (IQR)	10 (7–15)	9 (7–12)	0.545*
Hospitalization			
No. of patients hospitalized, *n* (%)	93 (62)	62 (71)	0.119†
Hospitalization, d, median (IQR)	5 (4–7)	6 (4–8)	0.034*
Indications for surgery			
Persistent abscess formation, *n* (%)	1 (1)	1 (1)	1.000†
Secondary testicular infarction, *n* (%)	3 (2)	1 (1)	
Recurrences			
Recurrent epididymitis within a 3-mo period, *n* (%)	1 (1)	3 (3)	0.141†
Three-month outcome in 178 patients	$n = 117$	$n = 61$	
WBC, giga/l, median (IQR)	6.8 (5.7–9.0)	7.0 (5.7–8.7)	0.530*
CRP, mg/l, median (IQR)	1.5 (0.5–3.6)	2.4 (0.5–6.9)	0.038*
PSA, ng/ml, median (IQR)	0.9 (0.5–1.4)	0.8 (0.5–2.1)	0.760*
Patients with bacterial pathogens, *n* (%)	17 (15)	9 (15)	1.000†
Patients with scrotal wall induration§, *n* (%)	0 (0)	0 (0)	1.000†
Patients with testicular pain§, *n* (%)	0 (0)	0 (0)	1.000†
Patients with epididymal pain§, *n* (%)	1 (1)	0 (0)	1.000†
Patients with persistent epididymal enlargement§, *n* (%)	19 (16)	10 (16)	1.000†

CRP = C-reactive protein; IQR = interquartile range; PSA = prostate-specific antigen; WBC = white blood cell count.
^ Levofloxacin ($n = 181$), ciprofloxacin ($n = 26$), moxifloxacin ($n = 2$).
‡ Chi-square test.
† Fisher exact test.
* Mann-Whitney *U* test.
§ Patients with semicastration excluded.

Hospitalization (7 vs 5 d) and total duration of antibiotic therapy (14 vs 12 d) were significantly increased in patients with a change of antibiotics ($p < 0.001$ and $p = 0.021$, respectively; Mann-Whitney *U* test). Finally, patients with indwelling urinary catheters required more intense and longer therapy (Supplementary Table 6).

3.5. Outcome after 3 mo

Semicastration had to be performed in only 6 of 237 patients (2.5%) due to secondary testicular infarction ($n = 4$) or persistent epididymal abscess formation with testicular involvement ($n = 2$) (Table 3). In these six patients (three with *E coli*, three with *Pseudomonas* spp), bacterial species in urine and tissue specimens were identical in four cases without showing resistance to the antibiotic used (Supplementary Table 7).

After an average of 94 d (IQR: 85–127) from the baseline visit, 178 of 237 patients (75%) were available for a late follow-up investigation. At this point, systemic inflammatory markers (WBC, CRP) normalized and patients in both groups were free of symptoms, although 29 patients (16%) still had evidence of persistent epididymal enlargement (Table 3). Asymptomatic bacteriuria was detected in 26 patients (15%) and significantly associated with the presence of indwelling transurethral catheters ($n = 9$; $p < 0.001$; Fisher exact test) (Supplementary Table 6).

On average, PSA levels in antibiotic-naive patients dropped to about half of the initial values in those cases with detected bacterial pathogens but remained more or less stable in those cases without evidence for bacterial pathogens. In pretreated patients, PSA levels declined to a similar extent, as witnessed in antibiotic-naive patients with pathogens, irrespective of whether a pathogen was

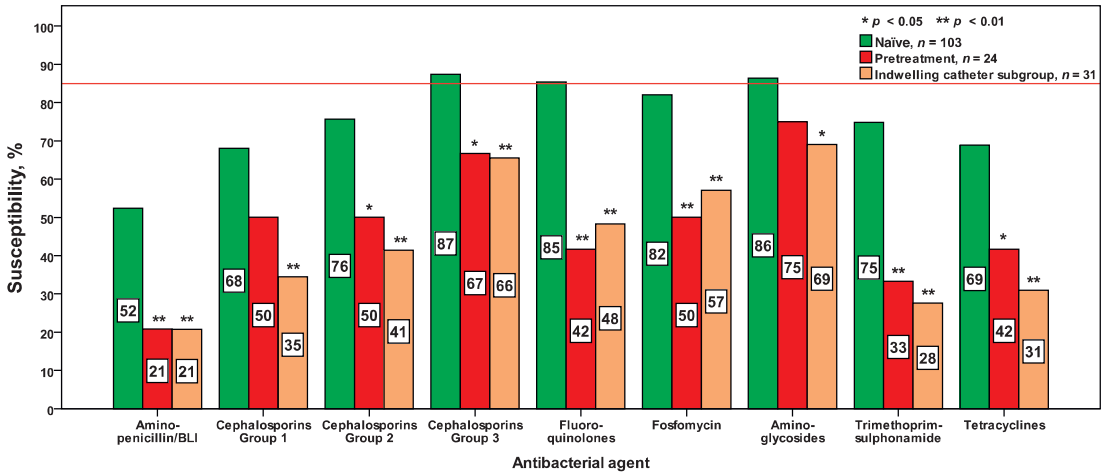

Fig. 2 – Susceptibility (percentage) of bacterial pathogens to different antibacterial agents. Green bars indicate results of 96 patients with 103 pathogens. Red bars show susceptibility of 24 pathogens isolated from 21 patients with antimicrobial pretreatment. Orange bars display results of 24 patients with indwelling urinary catheters harboring 31 pathogens. Red line indicates 85% susceptibility only for cephalosporins group 3, fluoroquinolones, and aminoglycosides in naive patients. The susceptibility is significantly lower in strains isolated from pretreated patients and from those with indwelling urinary catheters compared with naive patients ($p < 0.05$ or $p < 0.01$; Fisher exact test).

detected or not (Fig. 3). In patients where pathogen detection was based on 16S rDNA analysis, PSA values declined to a comparable degree (Supplementary Fig. 5).

4. Discussion

In this study, we analyzed the etiology of acute epididymitis in antibiotic-naive and pretreated patients, applying a comprehensive stepwise diagnostic work-up and describing the implications for antimicrobial therapy and patient management.

A bacterial etiology was evident in 87% of antibiotic-naive patients and 51% of pretreated patients. In contrast to previous studies [2,8,10,11,13,14,22,24], we explicitly included patients already on antimicrobial therapy (but requesting further treatment) to answer the question of whether bacterial pathogens play any role in such cases.

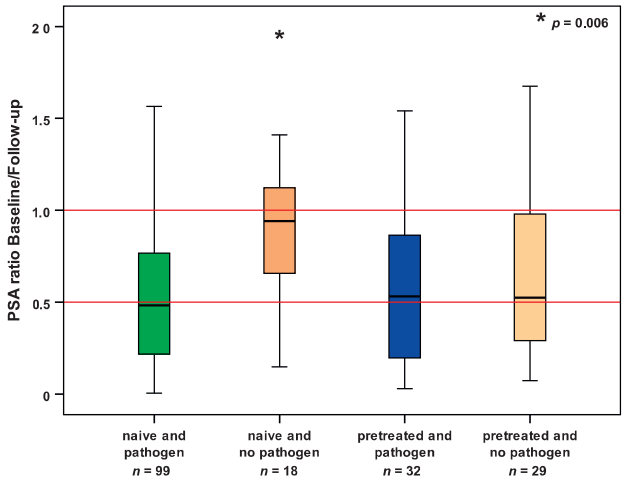

Fig. 3 – Prostate-specific antigen (PSA) ratio of baseline and 3-mo follow-up values with respect to bacterial pathogen identification and pretreatment in 178 patients. PSA declines to about 50% of baseline levels in naive patients with proven bacterial pathogen. PSA is virtually unaltered in naive patients without any bacterial pathogen. PSA declines in patients with antimicrobial pretreatment to levels comparable to those of naive patients with pathogens, regardless of whether or not a pathogen was detected.
PSA = prostate-specific antigen.

Early landmark studies showed homology of bacteria from urine specimens to those obtained from the epididymis by puncture/biopsy [8,9]. Because such procedures are obsolete due to postinterventional epididymal obstruction, we studied PSA as a noninvasive marker of prostatic involvement for demonstrating pathogen ascension [25]. In antibiotic-naive pathogen-positive patients, follow-up data revealed a PSA decrease to about 50% of baseline values. Interestingly, PSA values declined comparably in patients with antimicrobial pretreatment irrespective of bacterial pathogen status, suggesting ascending infection. In contrast, PSA was not altered in naive patients without detection of bacterial pathogens. This indicates that bacterial ascending infection is unlikely to be the cause of acute epididymitis in this group.

We enrolled patients with a wide age range from an unselected population who came to the general emergency department of our university hospital. Consequently, the resulting data were not limited to patients with STIs, as reported by other studies performed in army hospitals and STI clinics [8,10,11,17,21]. We also could show that the idea of an age limit attributing STIs to patients aged <35 yr and enteric pathogens to those aged >35 yr is debatable. Although sexual history suggesting STIs was significantly associated with the actual presence of STIs, about half of all STI pathogens were detected in sexually active patients who did not report such risks. This underlines the necessity to screen all sexually active patients for STIs [5,6].

Because studies on viral etiology are scarce [8,14–16], we undertook extensive viral analysis in bacteria-negative patients. Considering the frequent asymptomatic shedding of the BK and Epstein-Barr viruses in the urogenital

secretions of males [26,27], only enteroviruses were deemed etiologically relevant in two patients. This finding confirms existing serologic data regarding boys with acute epididymitis [16]. Surprisingly, neither the mumps virus nor other viruses from the respiratory panel were ever identified in our study. Generally speaking, viral epididymitis appears to be a rare condition.

Adequate primary antimicrobial therapy is the key to preventing long-term epididymal and testicular damage. However, just a small number of studies (all published >15 yr ago) have focused on antibiotic treatment in patients with epididymitis [2,10,13,21,22,24]. With antibiotic resistance rates (especially those of fluoroquinolones and cephalosporins) increasing worldwide in the past few years [28–30], we aimed to provide new rational data on empirical antimicrobial therapy. Our susceptibility assessments indicated that >85% of bacterial strains were susceptible to both fluoroquinolones and third-generation cephalosporins in antibiotic-naive patients. Considering the lack of antichlamydial activity of third-generation cephalosporins, our results support the current guidelines that recommend fluoroquinolones with antichlamydial activity as the preferred therapy [3,4,6]. According to our comprehensive data, primary antimicrobial therapy usually does not need to be changed because only a few high-risk patients (eg, those with indwelling urinary catheters) require such a switch. Notably, even patients with epididymal abscess formation, a classical indication for semicastration, usually recovered with conservative therapy.

Our study has limitations that should be acknowledged. First, no susceptibility testing was performed in cases of STIs because diagnosis relied only on PCR analysis. Second, in contrast to a clinical trial, individual antimicrobial therapy was allowed, whereby empirical therapy was primarily undertaken with levofloxacin and additionally with cefotaxime in hospitalized patients. Third, follow-up investigations were restricted to 3 mo after first presentation. Fourth, to save resources, virologic investigations were carried out only in those patients with no evidence for bacterial pathogens.

5. Conclusions

Our study investigated diagnostic advances regarding the etiology of acute epididymitis and revisits EAU/CDC guideline recommendations. Using state-of-the-art methods, we were able to show that (1) bacterial pathogen ascension is evident in up to 87% of cases, (2) 16S rDNA analysis improves pathogen detection and classification, (3) historical attribution of STIs to patients aged <35 yr and enteric pathogens to those aged >35 yr is not adequate, (4) viral epididymitis seems to be a rare condition, and (5) current guideline recommendations on empirical antimicrobial therapy are rational.

Author contributions: Adrian Pilatz had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Obtaining funding: Pilatz.

Administrative, technical, or material support: Chakraborty, Weidner.

Supervision: Wagenlehner, Weidner.

Other (specify): None.

Financial disclosures: Adrian Pilatz certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Florian Wagenlehner receives grants from Deutsche Forschungsgemeinschaft, Hessische Landesoffensive, European Association of Urology Research Foundation, Astellas, AstraZeneca, Bionorica, Cubist, Merlion, Leo Pharma, OM-Pharma, Pierre Fabre, Rosen Pharma, and Zambon.

Funding/Support and role of the sponsor: This work was supported by start-up funding for Adrian Pilatz (Medical Faculty, Justus Liebig University, Germany). The sponsor had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgment statement: The authors would like to thank Peter Ottway for copyediting the text.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2014.12.005.

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