DIAGNOSIS AND TREATMENT OF MALE ACCESSORY GLAND INFECTIONS

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Andrological Causes for Infertile Partnership

- Hypogonadism
- Testicular failure
- Obstruction
- Infection
- Idiopathic

Andrological Factor

OAT-S.

20% to 30%

Hypogonadism
Testicular failure
Obstruction
Infection
Varicocele
Disorders of ejaculation

Causes of Male Infertility

Idiopathic 31.7%
Cryptorchidism 5.8%
Systemic 5%
Immunologic 4.2%
Tumors 2.3%
Obstruction 1.5%
Malformations 5.8%
Cryptorchidism 8.5%
Hypogonadism 8.9%
Infections 9%
Others 6.5%
Varicocele 16.6%
Others 6.5%

n = 7802 patients

E. Nieschlag et al., 1997; Andrology, Springer-Verlag
Diagnosis of consecutive 1834 Men with Fertility Problems

- OAT-syndrome (n=635) 34.6%
- general diseases (n=35) 1.9%
- gynecomastia (n=28) 1.5%
- normal (n=52) 2.8%
- endocrine disorders (n=14) 0.8%
- varicocele (n=243) 13.2%
- testicular disorders (n=449) 24.5%
- ejaculatory disorders / sexual dysfunction (n=34) 1.9%
- infections / inflammation (n=155) 8.5%
- obstructive azoospermia (n=126) 6.9%
- immunological disorders (n=61) 3.3%
- cryopreservation (n=2) 0.1%

Andrological Outpatient Department Urology Giessen (2008)
Infections and Male Infertility

- acute and chronic urogenital infections (frequent)
  - Orchitis and Epididymitis
  - Prostatitis, Chronic Pelvic Pain Syndrome
  - MAGI
  - (Urethritis)
- generalized systemic infections (rare)
Epididymo-Orchitis

- Swelling, STD and UTI, chronic inflammation

Ultrasonography

- Recent results: 100 consecutive patients -> 70% positive microbiology

Biopsy

Pilatz et al., 2009 in press
Testicular Inflammation and Spermatogenesis

sperm density

3 - 12 weeks
time

normozoospermia

oligozoospermia

azoospermia
# Spermatological Outcome of Acute Epididymo-Orchitis

<table>
<thead>
<tr>
<th>OAT - Syndrom</th>
<th>Testicular azoospermia</th>
<th>Obstructive (Epididymal) azoospermia</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 %</td>
<td>&lt; 1 %</td>
<td>&lt; 5 %</td>
</tr>
</tbody>
</table>

Weidner et al., Human Reproduction Update, 1999
Diemer and Desjardins, Encyclopedia of Reproduction, 1999
Paavonen and Eggert-Kruse, Human Reproduction Update, 1999
Chronic Inflammation in Testicular Biopsies
Azoospermia

- Up to 14% peritubular lymphocyte-inflammation
- Mast-cell increase
- Interaction to dendritic cells
- Association to spermatogenetic failure

- Direct association to bacterial origin is lacking -

¹ Schuppe and Meinhardt, 2008
² Bhushan et al., 2008
### Prostatitis

**NIDDK / NIH Classification**

<table>
<thead>
<tr>
<th>I</th>
<th>Acute Bacterial Prostatitis (ABP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Chronic Bacterial Prostatitis (CBP)</td>
</tr>
<tr>
<td>III</td>
<td>Chronic Pelvic Pain Syndrome (CPPS)</td>
</tr>
<tr>
<td>A</td>
<td>Inflammatory (EPS, VB III, Semen)</td>
</tr>
<tr>
<td>B</td>
<td>Non - inflammatory</td>
</tr>
<tr>
<td>IV</td>
<td>Asymptomatic (inflammatory)</td>
</tr>
</tbody>
</table>

Krieger et al., JAMA 292: 236 (1999)
GIESSEN COHORT STUDIES

Study 1992
1985-1990
n = 656

NIH IIIA
31.0% (n=203)

NIH IIIB
51.0% (n=335)

NIH II
4.2% (n=7)

UP
11.0% (n=72)

Study 2002
2001-2002
n = 168

NIH IIIA
31.5% (n=53)

NIH IIIB
50.0% (n=84)

NIH II
14.3% (n=24)

UP
14.3% (n=24)
1. Urine
Mid-stream Urine
10
EPS
Urine after prostatic massage
DIAGNOSTIC MANAGEMENT

INFECTIONS

- NIH I  urine analysis, culture
- NIH II  4 and 2 glass test, semen culture, (significant bacteriospermia in about 50%)
- NIH III 4 and 2 glass test are an indicator for inflammation and infection
- NIH IV  no suggestion

Paris, 2005
Consensus Conference NIH, EAU, WHO
INFLUENCE OF LEUKOCYTES IN THE EJACULATE ON CP / CPPS CLASSIFICATION

n=140

Traditional
• EPS, VB3
NIH IIIA 28 %
NIH IIIB 72 %

New: EPS, VB3 + Semen
NIH IIIA 52 %
NIH IIIB 48 %

1.9 fold more patients to have inflammatory CP / CPPS

Krieger et al., 2003
Bacteriospermia in CBP

(≥10³ cfu/ml)

<table>
<thead>
<tr>
<th><strong>Ejaculate quality</strong></th>
<th>no influence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evidence of leukocytes</strong></td>
<td>Improves the accuracy for classification in category IIIa and IIIb</td>
</tr>
<tr>
<td><strong>Autoimmune markers</strong> (complement, T-cells) Immunoglobulines cytokines</td>
<td>only research</td>
</tr>
</tbody>
</table>
Cutpoints for EPS, urine after P.M. (VB3) and ejaculate/seminal plasma parameters indicative for inflammation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cutpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPS leukocytes</td>
<td>≥ 10-20/1000 x</td>
</tr>
<tr>
<td>VB3 leukocytes</td>
<td>≥ 10/mm³</td>
</tr>
<tr>
<td>Semen PPL</td>
<td>≥ 0.113 x 10⁶/ml</td>
</tr>
<tr>
<td>Seminal plasma Elastase</td>
<td>≥ 280 ng/ml</td>
</tr>
<tr>
<td>Seminal plasma IL-8</td>
<td>&gt; 10600 pg/ml</td>
</tr>
</tbody>
</table>

Wagenlehner and Weidner, 2008
### Inflammatory Parameters in CP/CPPS and Infertile Men

<table>
<thead>
<tr>
<th></th>
<th>NIH IIIa N34</th>
<th>NIH IIIb N140</th>
<th>Infertile Men N77</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>45 (19-69)</td>
<td>42 (18-69)</td>
<td>40 (15-71)</td>
</tr>
<tr>
<td><strong>PPL (mill./ml)</strong></td>
<td>0.23 (0-8.24)</td>
<td>0.04 (0-12.08)</td>
<td>0.07 (0-23.04)</td>
</tr>
<tr>
<td><strong>Elastase (ng/ml)</strong></td>
<td>188 (7-1.708)</td>
<td>95 (4-1001)</td>
<td>91 (2-400)</td>
</tr>
<tr>
<td><strong>IL-8 (pg/ml)</strong></td>
<td>2,969 (27-10,001)</td>
<td>1,588 (7 – 10,001)</td>
<td>1,602 (13-10,001)</td>
</tr>
</tbody>
</table>

ongoing study
Wagenlehner et al.
Dresden 2009
### Altered Sperm Parameters and "Prostatitis"

<table>
<thead>
<tr>
<th>Sperm Parameter</th>
<th>Proven</th>
<th>Questionable</th>
<th>No hint</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteriospermia</td>
<td>+</td>
<td></td>
<td></td>
<td>CBP</td>
</tr>
<tr>
<td>OAT-S.</td>
<td></td>
<td>+</td>
<td></td>
<td>totally unclear</td>
</tr>
<tr>
<td>Leucocytospermia</td>
<td>+</td>
<td></td>
<td></td>
<td>CBP, NIH IIIa</td>
</tr>
<tr>
<td>Cytokine response</td>
<td>+</td>
<td></td>
<td></td>
<td>NIH IIIa</td>
</tr>
<tr>
<td>ROS formation</td>
<td></td>
<td>+</td>
<td></td>
<td>no new data</td>
</tr>
<tr>
<td>Sperm antibodies</td>
<td></td>
<td></td>
<td>-</td>
<td>recently reconfirmed</td>
</tr>
<tr>
<td>Inflammatory obstruction</td>
<td>(+)</td>
<td></td>
<td></td>
<td>rare</td>
</tr>
</tbody>
</table>
Male Accessory Gland Infection

- Asymptomatic (silent ejaculate infection)
- Leukocytospermia

WBC > 1 x 10^6/ml
Peroxidase Staining

Unsolved Problems of Leukocytospermia

- Only associated with bacterial infections in 20%
- High rate of spontaneous resolution in infertile men

WHO, WHO Manual
Cambridge University Press, 1992
## MAGI – CLASSIFICATION SYSTEM

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical History/Physical Signs</td>
<td>Urine after P-Massage</td>
<td>Ejaculate signs</td>
</tr>
<tr>
<td>e.g. UTI, Epididymitis, STD</td>
<td>Increased PML</td>
<td>PPL</td>
</tr>
<tr>
<td>Epididymal swelling</td>
<td>C. trachomatis</td>
<td>Bacteriospermia</td>
</tr>
<tr>
<td>Abnormal prostate</td>
<td></td>
<td>C. trachomatis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biochemistry</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inflammation</td>
</tr>
</tbody>
</table>

**C. trachomatis PCR**
- PPL > 1 Mill./ml
- Bacteriospermia > 1000 cfu/ml
- Elastase > 250 ng/ml

**MAGI =**
- a) 2 signs, each from a different group
- b) at least 2 ejaculate signs

(WHO 1993, 2000)
PATIENTS / METHODS

- 258 infertile men (age 24-69 years)
- Ejaculate analysis according to WHO
  - analysis of PPL (1 Mill./ml), bacteria (10³ cfu/ml), elastase (250 ngl/ml)
- Exclusion of urethritis (1. voided urine: PML, C. trachomatis, N. gonorrhoeae)
- Diagnosis of NIH II prostatitis and CP/CPPS
  - NIH-CPSI, 4-glass-technique
- Diagnosis of chronic epididymitis
  - palpation, scrotal ultrasonography
RESULTS

DIAGNOSIS OF UROGENITAL INFECTION / INFLAMMATION

n = 258

MAGI

63 (24.4 %)

including
25 epididymitis
14 urethritis

NIH

101 (39.1 %)
RESULTS

DIAGNOSIS OF PROSTATE RELATED INFECTION / INFLAMMATION

n 258

MAGI
24 (9 %)
excluding
25 epididymitis
14 urethritis

NIH
62 (24 %)

“prostatitis“
NIH II 26 (10 %)
NIH IIIa 36 (14 %)
## RESULTS

**EJACULATE DIAGNOSIS OF UROGENITAL INFECTION / INFLAMMATION IN DEFINED ENTITIES**

<table>
<thead>
<tr>
<th>Entity</th>
<th>n</th>
<th>Bacteriospermia</th>
<th>PPL</th>
<th>Elastase</th>
<th>C. trachomatis</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH II</td>
<td>26*</td>
<td>none **</td>
<td>12</td>
<td>15</td>
<td>none</td>
</tr>
<tr>
<td>NIH Illa</td>
<td>36</td>
<td>none</td>
<td>24</td>
<td>20</td>
<td>none</td>
</tr>
<tr>
<td>Epididymitis</td>
<td>25</td>
<td>9</td>
<td>9</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Urethritis</td>
<td>14</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>12</td>
</tr>
</tbody>
</table>

* 15 x E. Coli

** xx > 10³ cfu/ml
CONCLUSIONS

- The WHO diagnosis „MAGI“ detects urogenital infection/inflammation in about 20% of patients.

- In this figure, cases of epididymitis and urethritis are included.

- Prostate related infections (NIH II) are detectable in 10% of infertile men.

- Questionable prostate-related inflammatory changes (NIH IIIa) have to be noted in further 14%.

  Ejaculate analysis demonstrates leukocytal activity in about two thirds of these cases.

- The MAGI classification of the WHO clearly underestimates the percentage of infections/inflammatory prostatitis and/or CP/CPPS in male infertility.
CONCLUSIONS

To exclude male urogenital infections and inflammation in infertile men

- ejaculate analysis
- clinical investigation of the epididymis
- a 4 glass test for prostatitis diagnosis

are mandatory.
THERAPEUTIC DILEMMA

- Antibacterial therapy works in about 70%
- The persistence of inflammation can not be predicted.
**SUGGESTED ANTIBIOTIC IN CBP (NIH II)**

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Choices</th>
</tr>
</thead>
<tbody>
<tr>
<td>fluoroquinolones</td>
<td>1. choice</td>
</tr>
<tr>
<td>trimethoprim / sulfamethoxazole</td>
<td>in FQ resistance (2-3 months)</td>
</tr>
<tr>
<td>macrolides</td>
<td>gram positives, atypical m.</td>
</tr>
<tr>
<td>tetracyclines</td>
<td>atypical m.</td>
</tr>
<tr>
<td>aminoglycosides</td>
<td>not suggested</td>
</tr>
</tbody>
</table>

EAU guidelines 2009
# Fluoroquinolones in CBP

<table>
<thead>
<tr>
<th></th>
<th>Dosage/day (mg)</th>
<th>Days</th>
<th>n</th>
<th>Eradication (%)</th>
<th>Follow up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norfloxacin</td>
<td>800</td>
<td>28</td>
<td>14</td>
<td>64</td>
<td>6</td>
</tr>
<tr>
<td>Schaeffer et al</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1990</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>4-800</td>
<td>174</td>
<td>42</td>
<td>60</td>
<td>8</td>
</tr>
<tr>
<td>Petrikkos et al</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1991</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400</td>
<td>14</td>
<td>21</td>
<td>67</td>
<td>12</td>
</tr>
<tr>
<td>Pust et al</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1989</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1000</td>
<td>14</td>
<td>15</td>
<td>60</td>
<td>12</td>
</tr>
<tr>
<td>Weidner et al</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1987</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1000</td>
<td>28</td>
<td>16</td>
<td>63</td>
<td>21-36</td>
</tr>
<tr>
<td>Weidner et al</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1991</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1000</td>
<td>60-150</td>
<td>7</td>
<td>86</td>
<td>12</td>
</tr>
<tr>
<td>Pfau</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1987,1991</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1000</td>
<td>28</td>
<td>34</td>
<td>76</td>
<td>6</td>
</tr>
<tr>
<td>Naber et al</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2000</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1000</td>
<td>28</td>
<td>78</td>
<td>72</td>
<td>6</td>
</tr>
<tr>
<td>vs. Lomefloxacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2001</td>
</tr>
<tr>
<td>Naber et al</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2001</td>
</tr>
<tr>
<td>Lomefloxacin</td>
<td>400</td>
<td>28</td>
<td>75</td>
<td>63</td>
<td>6</td>
</tr>
<tr>
<td>Naber et al</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2001</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500</td>
<td>28</td>
<td>136</td>
<td>53</td>
<td>6</td>
</tr>
<tr>
<td>Bundrick et al</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2003</td>
</tr>
<tr>
<td>Naber et al</td>
<td>500</td>
<td>28</td>
<td>116</td>
<td>84</td>
<td>6</td>
</tr>
</tbody>
</table>

Meares & Stamey - Diagnosis
NIH II

- NIH II: antibiotics, $\alpha$-blockers (4 weeks) → 63-76% bacteriological cure

- failure
  - intermittent antimicrobial therapy (acute symptomatic)
  - low dose suppression
  - radical TUR-P or prostatectomy

Paris 2005
Sperm Preparation: Glasswool

TARGETS OF THERAPY

• Eradication of Microorganisms

• Normalization of Inflammatory Parameters

Normalization of Symptoms
Bacteria - Sperm - Interaction

Motility and Morphology

Agglutination

Adhesion

Membrane damage

Diemer, Weidner et al.,
Andrologia 35: 100 (2003)
Bacteria - Sperm - Interaction

Motility and Morphology

Depending upon

- **Species**
  - + E. coli, C. trachomatis
  - - E. faecalis, Staphylococcus spp.

- **Number**
  - Andrologia 35: 100 (2003)

- **Time**
Bacteriospermia

cfu/ml vs. frequency of ejaculation