Diagnosis and treatment of chronic prostatitis

Conference Paper · November 2011

CITATIONS
0

READS
311

1 author:

Goran Stimac
University Clinical Hospital Center "Sestre Milosrdnice"
124 PUBLICATIONS **301** CITATIONS

SEE PROFILE

Diagnostics and treatment of chronic prostatitis (current recommendations and new prospects)

Goran Štimac

Clinical Department of Urology,
"Sestre milosrdnice"
University Hospital Center,
Zagreb, Croatia

2nd SEEC, Belgrade, November 2011

Stamey TA.

"Pathogenesis and treatment of urinary tract infections", Baltimore: Williams & Wilkins, 1980.

"Prostatitis is a wastebasket of clinical ignorance!"

PROSTATITIS - HYSTORY

1922. - Farman - prostatic massage

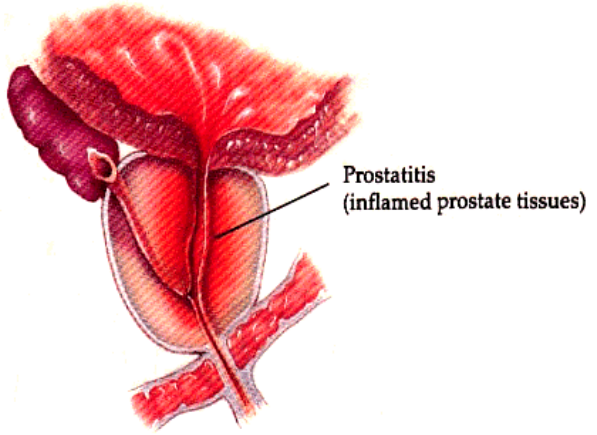
1930. - sulphonamides - antimicrobial therapy

1968. - Meares, Stamey – 4 - glass test

2000. - DaMarzo, Nelson -
inflammation and prostate carcinogesis

PROSTATITIS IS AN INFLAMMATORY CONDITION OF THE PROSTATE THAT PRESENTS WITH:

- **urethral symptoms**
  (painful voiding, urinary urgency, frequency, nocturia, dysuria, etc.)
- **prostatic symptoms**
  (pain and discomfort in the low back, perineal, suprapubic, groin areas, etc.)
- **sexual symptoms**
  (erectle dysfunction, ejaculatory dysfunction, etc.)
- **other symptoms**
  (fatigue, myalgia, headache, etc.)



EPIDEMIOLOGY – PROSTATITIS SYNDROMES

- **Account for 1/4th of all male office visits for genitourinary symptoms** (Schappert, 1994).
- **50% of all men – prostatitis symptomes during lifetime.**
- **Most common urologic diagnosis in men <50, and third most in men >50** (Collins, 1998).
- **Overall prevalence: 9% (like ischaemic heart disease)** (Wenninger, 1996).
- **Sickness impact equivalent to AMI, Crohn's or angina** (Wenninger, 1996).

CLASSIFICATION OF PROSTATITIS SYNDROMES

Table 10.5: Classification of prostatitis according to Drach et al (23)

1978.

Classification	Clinical and laboratory findings
Acute bacterial prostatitis	Clinically significant infection of the prostate
Chronic bacterial prostatitis	Significant inflammation of the prostate Isolation of an aetiologically recognised organism from the prostatic fluid/urine
Chronic abacterial prostatitis	Significant prostatic inflammation Failure to isolate an organism from the prostatic fluid/urine, or isolation of an organism whose aetiological significance is debatable
Prostatodynia	No significant prostatic inflammation Failure to isolate an organism from the prostatic fluid/urine

Table 10.3: Classification of prostatitis and CPPS according to NIDDK/NIH (3-5)

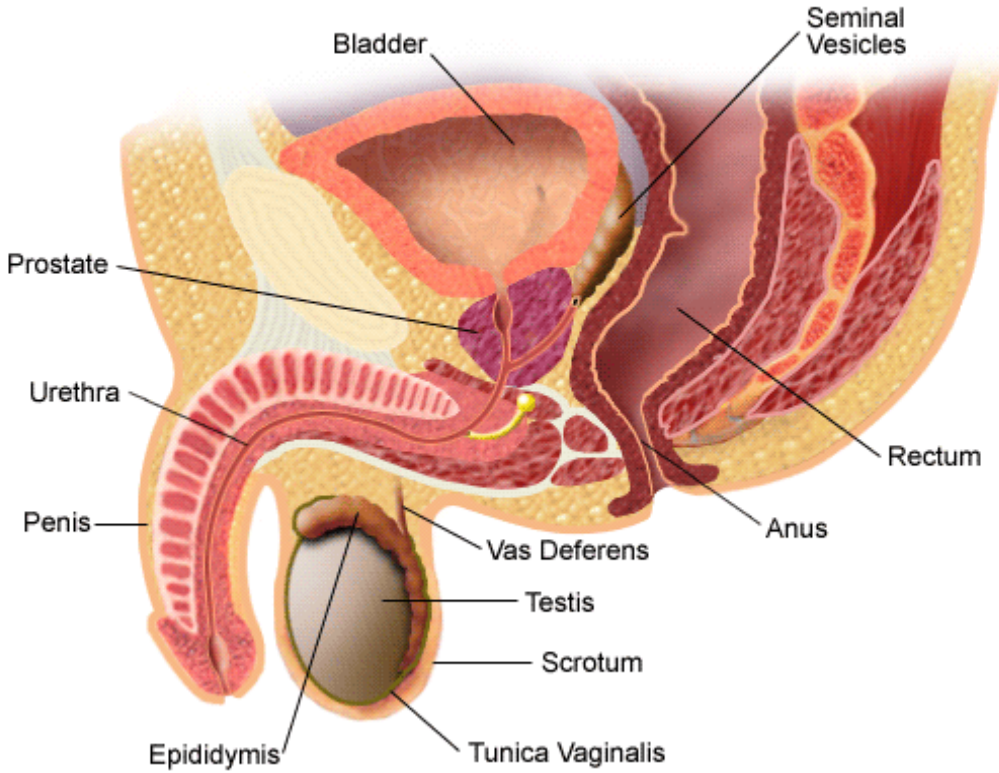
1995.

Type	Name and description
I	Acute bacterial prostatitis
II	Chronic bacterial prostatitis
III	Chronic abacterial prostatitis - CPPS A. Inflammatory CPPS (white cells in semen/EPS/VB3) B. Non-inflammatory CPPS (no white cells in semen/EPS/VB3)
IV	Asymptomatic inflammatory prostatitis (histological prostatitis)

CPPS = chronic pelvic pain syndrome; EPS = expressed prostatic secretion; VB3 = voided bladder urine 3 (urine following prostatic massage).

BACTERIAL PROSTATITIS - PATHOGENESIS

- **Ductal reflux, urethral ascension.**
- **Direct or lymphatic from rectum.**
- **Haematogenous.**



CHRONIC BACTERIAL PROSTATITIS (TYPE II)

CBP is a chronic or persistent infection of the prostate in which a patogen can be demonstrated by a lower urinary tract segmented localisation test, but in which systemic symptoms are absent.

Schaeffer et al. Ann Rev Med, 2006.

- **Most frequent cause of reccurent UTI in adult men (40 – 70 yrs).**
- **Asymptomatic periods with infection relapses.**
- **Symptoms should be present at least 3 months!!**

CAUSATIVE PATHOGENS

- **“traditional uropathogens” –**
  E.coli, P.mirabilis, Kl. pneumoniae, Ps.aeruginosa, Enterococci, Staph.aureus

- **“unusual”, “non-traditional uropathogens” –**
  C. trachomatis, Mycoplasma, U. urealyticum, Trichomonas vaginalis, staphylococci, streptococci − **still controversial!!**

- **biofilm disease**
  (biofilm − bacterial populations that are enclosed in a matrix of extracellular polymeric substances)

BASIC DIAGNOSTIC PROCEDURES FOR CHRONIC BACTERIAL PROSTATITIS

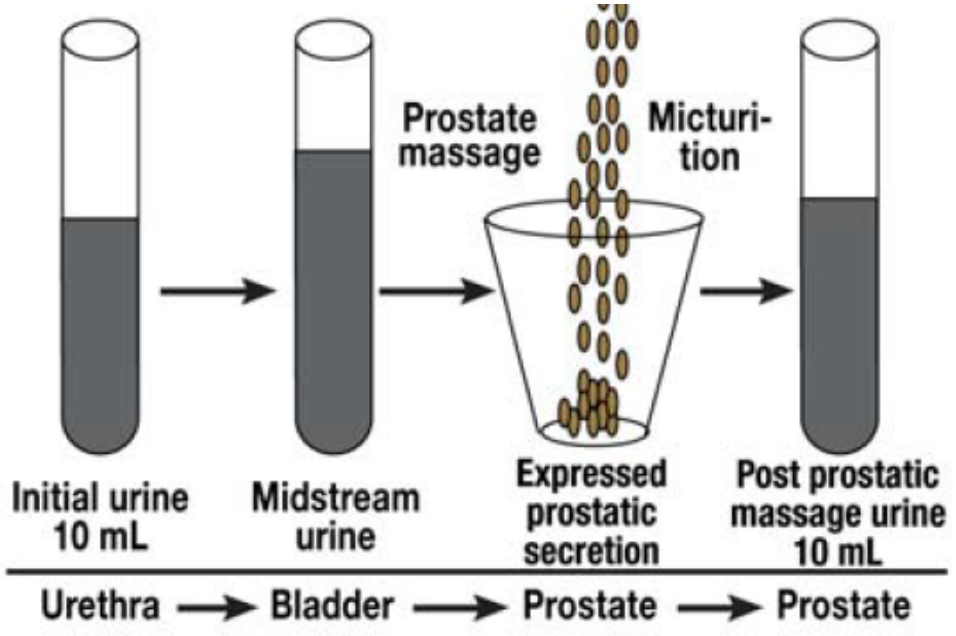
European Association of Urology

MANDATORY:

- Detailed history (clinical symptoms and signs).
- DRE – nonspecific.
- NIH-CPSI questionnaire.
- 4-glass test acording to Meares/Stamey or
  2-glass pre/post-massage test with culture and microscopy (WBC counts) (Nickel, 2002.)

OPTIONAL:

- Detection of unusual pathogens.
- Urethral swabs.
- Semen analysis and culture.
- Uroflowmetry with residual urine.
- Serum PSA.
- Transrectal ultrasound.



2-GLASS VS 4-GLASS TEST?

How Does the Pre-Massage and Post-Massage 2-Glass Test Compare to the Meares-Stamey 4-Glass Test in Men With Chronic Prostatitis/Chronic Pelvic Pain Syndrome?

Nickel JC et al. J Urol. 2006.

- **Both tests compared in detection of WBC and bacteria.**
- **The 2-glass test predicted a correct diagnosis in more than 96% of pts.**
- **It has strong concordance with the 4-glass test.**
- **Good alternative when expressed prostatic secretions are not obtained.**
- **Naber GK, Milan, Italy, 14 November 2008:**
  - **for correct diagnosis: 4-glass test necessary !**
  - **for screening purposes: 2-glass test!**

REVIEW ARTICLE

Prostatitis and Male Pelvic Pain Syndrome

Diagnosis and Treatment

Florian ME Wagenlehner, Kurt G Naber, Thomas Bschleipfer,
Elmar Brähler, Wolfgang Weidner

Deutsches Ärzteblatt International | Dtsch Arztebl Int 2009; 106(11):175–83

Criteria for the diagnosis of chronic bacterial prostatitis (1)

	2- or 4-glass test
Leukocytes (n)	$\geq 10/mm^3$ in post prostatic massage urine or $\geq 10/1000 \times$ expressed prostatic secretion
Bacteria (CFU/mL)	Post prostatic massage urine / expressed prostatic secretion $\geq 10 \times$ initial midstream urine
	Ejaculate
Leukocytes (n)	$>10^6$ PPL/mL
Bacteria	Not reliable

Chronic Prostatitis Symptom Index (CPSI) (NIH)

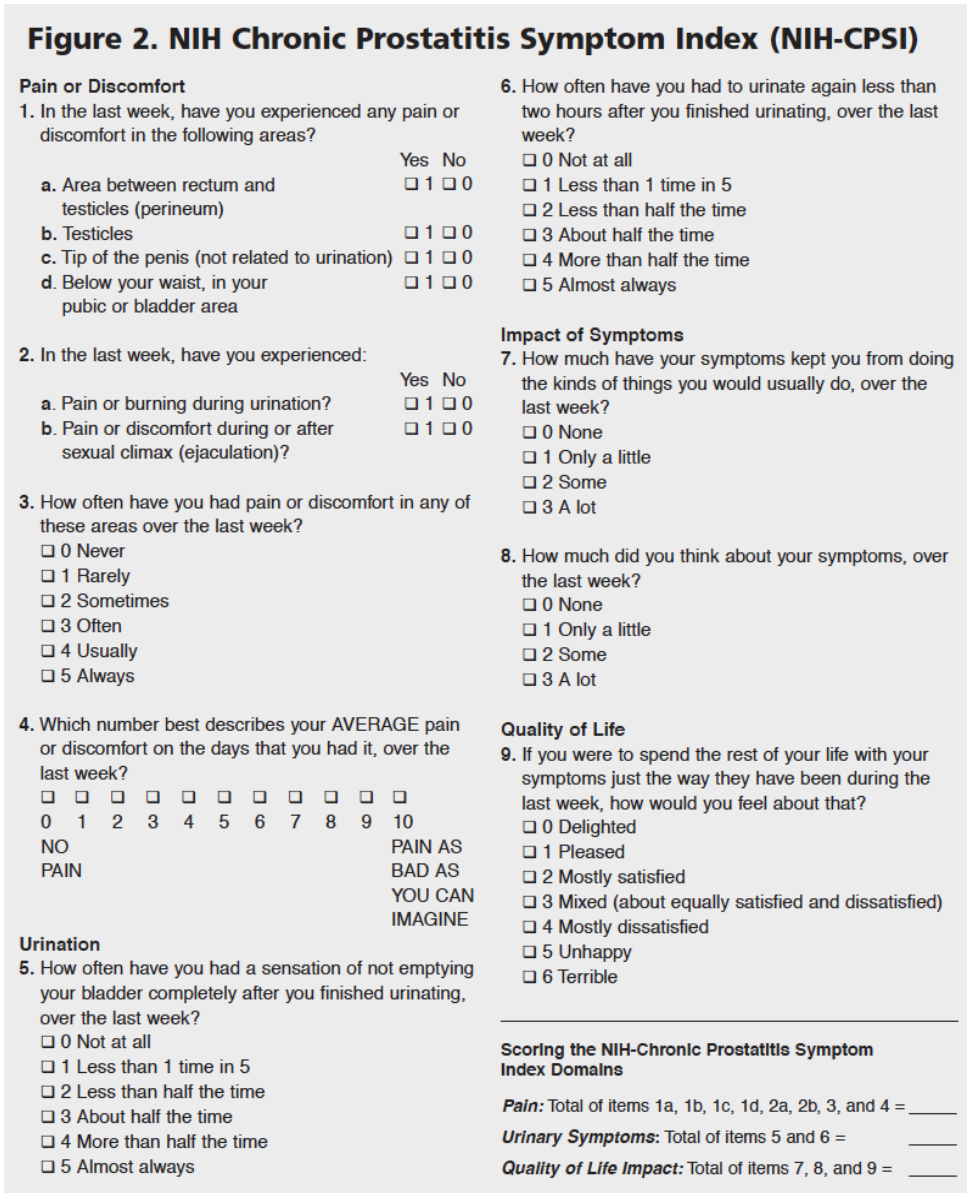


Figure 2. NIH Chronic Prostatitis Symptom Index (NIH-CPSI)

Pain or Discomfort

1. In the last week, have you experienced any pain or discomfort in the following areas?

	Yes	No
a. Area between rectum and testicles (perineum)	❑ 1	❑ 0
b. Testicles	❑ 1	❑ 0
c. Tip of the penis (not related to urination)	❑ 1	❑ 0
d. Below your waist, in your pubic or bladder area	❑ 1	❑ 0

2. In the last week, have you experienced:

	Yes	No
a. Pain or burning during urination?	❑ 1	❑ 0
b. Pain or discomfort during or after sexual climax (ejaculation)?	❑ 1	❑ 0

3. How often have you had pain or discomfort in any of these areas over the last week?
   - ❑ 0 Never
   - ❑ 1 Rarely
   - ❑ 2 Sometimes
   - ❑ 3 Often
   - ❑ 4 Usually
   - ❑ 5 Always

4. Which number best describes your AVERAGE pain or discomfort on the days that you had it, over the last week?

❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑
0 1 2 3 4 5 6 7 8 9 10
NO PAIN — PAIN AS BAD AS YOU CAN IMAGINE

Urination

5. How often have you had a sensation of not emptying your bladder completely after you finished urinating, over the last week?
   - ❑ 0 Not at all
   - ❑ 1 Less than 1 time in 5
   - ❑ 2 Less than half the time
   - ❑ 3 About half the time
   - ❑ 4 More than half the time
   - ❑ 5 Almost always

6. How often have you had to urinate again less than two hours after you finished urinating, over the last week?
   - ❑ 0 Not at all
   - ❑ 1 Less than 1 time in 5
   - ❑ 2 Less than half the time
   - ❑ 3 About half the time
   - ❑ 4 More than half the time
   - ❑ 5 Almost always

Impact of Symptoms

7. How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?
   - ❑ 0 None
   - ❑ 1 Only a little
   - ❑ 2 Some
   - ❑ 3 A lot

8. How much did you think about your symptoms, over the last week?
   - ❑ 0 None
   - ❑ 1 Only a little
   - ❑ 2 Some
   - ❑ 3 A lot

Quality of Life

9. If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?
   - ❑ 0 Delighted
   - ❑ 1 Pleased
   - ❑ 2 Mostly satisfied
   - ❑ 3 Mixed (about equally satisfied and dissatisfied)
   - ❑ 4 Mostly dissatisfied
   - ❑ 5 Unhappy
   - ❑ 6 Terrible

Scoring the NIH-Chronic Prostatitis Symptom Index Domains

Pain: Total of items 1a, 1b, 1c, 1d, 2a, 2b, 3, and 4 = _____

Urinary Symptoms: Total of items 5 and 6 = _____

Quality of Life Impact: Total of items 7, 8, and 9 = _____

- **Developed by the International Prostatitis Collaborative Network (IPCN) in 1999.**
- **Contains four questions regarding pain, two regarding urination, and three related to QoL.**
- **Still the best tool for outcome measures (NOT for diagnosis!)**

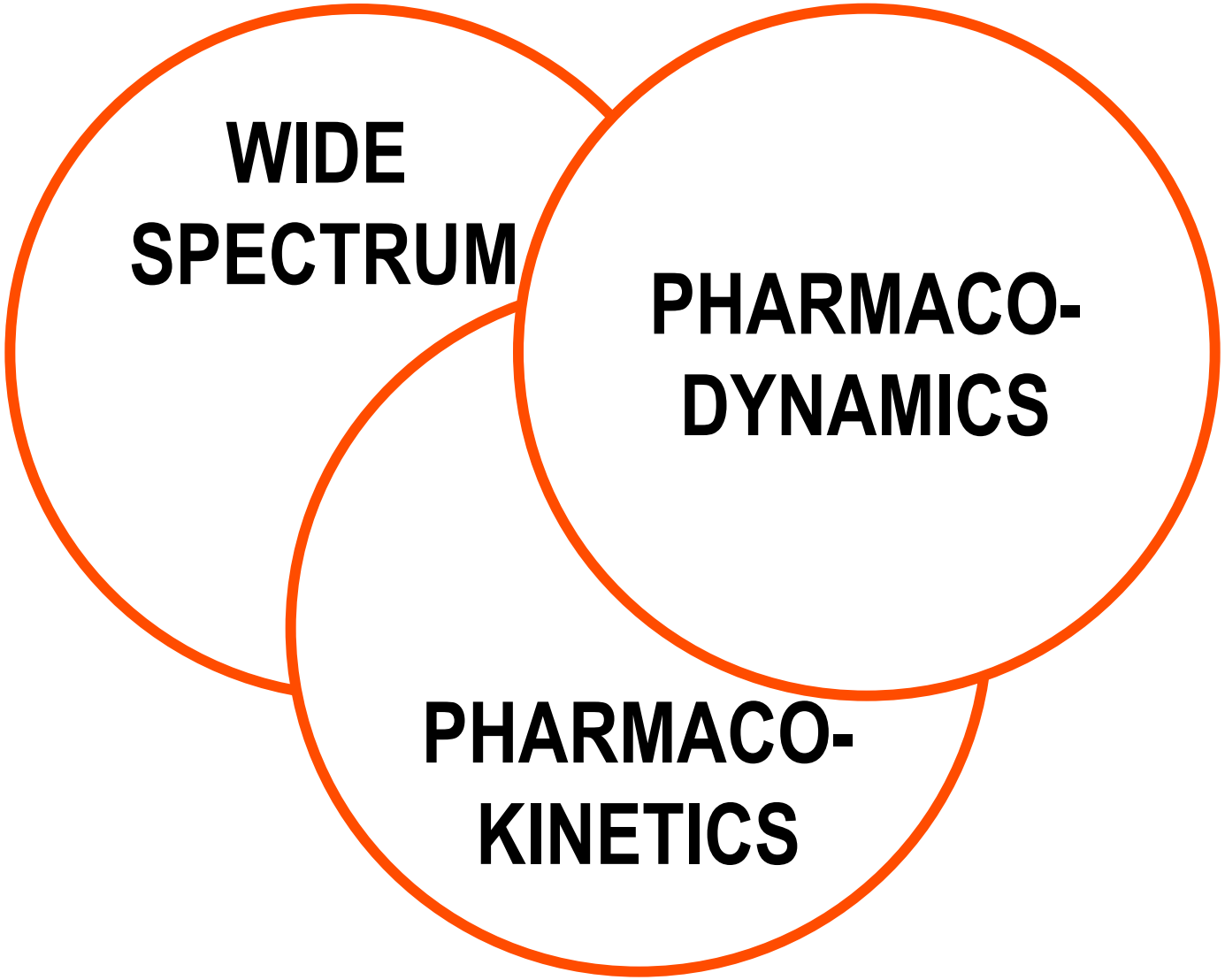
from: Litwin MS, McNaughton-Collins M, Fowler FJ Jr, Nickel JC, Calhoun MA, Pontari MA, Alexander RB, Farrar JT, O'Leary MP. The National Institute of Health chronic prostatitis symptom index: development and validation of new outcome measure. Chronic Prostatitis Collaborative Research Network. J Urol 1999:162;369-375.

CHRONIC BACTERIAL PROSTATITIS THERAPY

DRUGS	ROUTE/ DURATION/ NOTE
Fluoroquinolones (Ciprofloxacin, Levofloxacin, Ofloxacin, Maxifloxacin, Prulifloxacin)	Oral/ 4-6 weeks
Trimetophrim	Oral/ 4 weeks
Co-trimoxazole	Oral/ 4-6 weeks
Macrolides	Oral/ 4-6 weeks In combination with quinolones. Azithromycin 500mg/day is dosed only the first three days of each week of treatment
3rd gen. cephalosporins±aminoglykosides	
Alpha-adrenoceptor blockers	Oral/ 4 weeks – 6 months
NSAIDS	Oral/ 2-4 weeks
Steroid Anti-inflammatory agents	Oral/ Depending on symptom severity
Serenoa repens alone or combined with lycopene, selenium, Urtica dioica, quercetin, cureumin, etc.	Oral/ 4 weeks – 6 months
Thioctic acid	Oral/ Up to 8 weeks
Peptide complexes extracted from cattle prostate tissue	Rectal/ 4 weeks
Lyophilized bacterial lysate od Escherichia coli	Oral/ 4 months

Magri V, Perletty G et al. Critical issue in chronic prostatitis. Arch Ital Urol Androl 2010;82:75-82.

FIRST LINE TREATMENT - FLUOROQUINOLONES



OPTIMAL MANAGEMENT OF CBP CAUSED BY NONTRADITIONAL PATHOGENS

FIRST CHOICE

- **AZITHROMYCIN** in a total dose:
  - 4,5g oral, during 3 weeks, administered for 3 days weekly in doses 1x500mg per day (PULSE THERAPY) or
  - 4 g oral, during 4 weeks, administered one day weekly as a single 1000 mg dose (PULSE THERAPY).

SECOND-LINE OPTIONS (in case of chemoresistance or intolerance)

- **DOXYCYCLINE** 100mg oral, twice-daily, for 3-4 weeks.

Škerk V et al. Comparative analysis of azithromycin and clarithromycin efficacy and tolerability in the treatment of chronic prostatitis caused by Chlamydia trachomatis. J Chemother 2001;14:384-9.

Škerk V et al. Comparative analysis of azithromycin and ciprofloxacin in the treatment of chronic prostatitis caused by Chlamydia trachomatis. Int J Antimicrob Agents 2003;21:457-62.

Škerk V et al. Comparative randomized pilot study of azithromycin and doxycycline efficacy in the treatment of prostate infection caused by Chlamydia trachomatis. Int J Antimicrob Agents 2004;24:188-91.

Škerk,V et al. Azithromycin: 4.5- or 6.0-gram dose in the treatment of patients with chronic prostatitis caused by Chlamydia trachomatis--a randomized study. J Chemother 2004;16:408-10.

DURATION OF THERAPY

AT LEAST 4 WEEKS
TO PREVENT RELAPSE AND
LONG TERM SEQUELAE!

(Nickel, 1999.)

DURATION OF THERAPY – PITFALLS?

40% OF UROLOGISTS AND
65% OF GPs PROSCRIBE THERAPY
FOR LESS THAN TWO WEEKS ?!

ONLY 40% TO 60% OF PATIENTS
RESPOND TO LONG TERM
ANTIBIOTIC THERAPY ?!

(Nickel, 1997.)

CHRONIC PELVIC PAIN SYNDROME - CPPS (TYPE III)

CPPS is a clinical entity defined as urologic pain or discomfort in the pelvic region, associated with urinary symptoms and/or sexual dysfunction, without demonstration of uropathogenic bacteria lasting for at least 3 of the previous 6 months.

Nickel et al. JAMA, 2011.

IT IS A DIAGNOSIS OF EXCLUSION!

RULE OUT EVERYTHING!

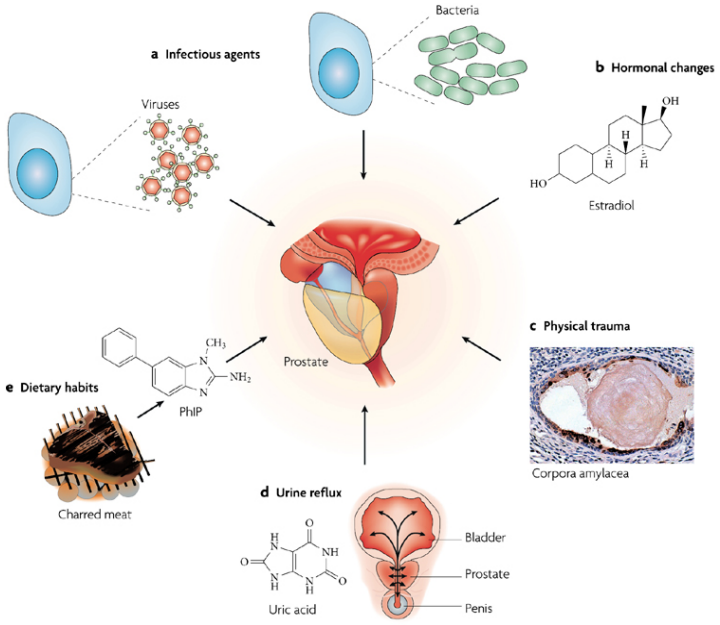
(malignancy, BPH, stone disease, neurogenic bladder, urethral stricture, anomaly, systemic disease, etc.)

CPPS (TYPE III)

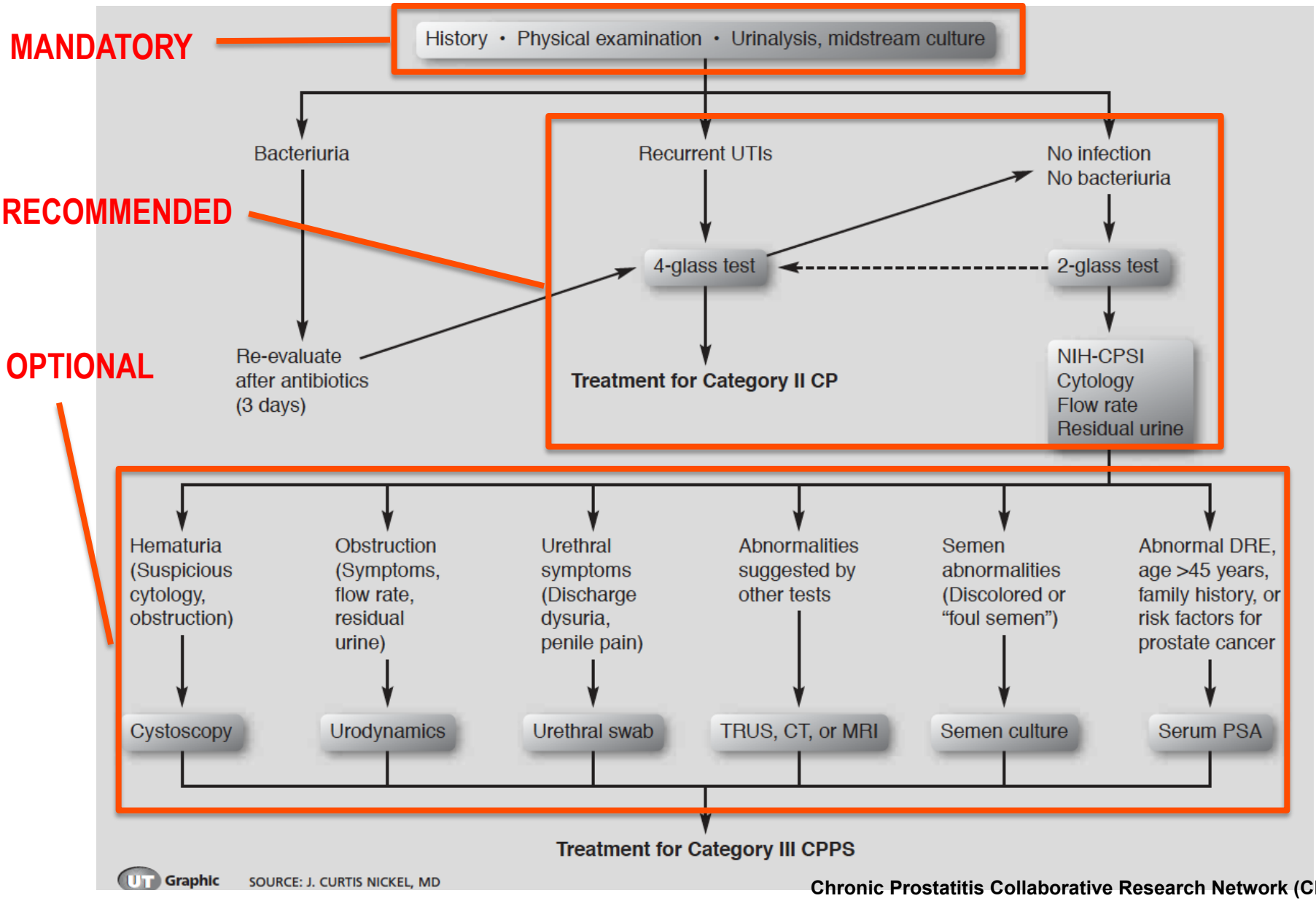
- Most common prostatitis syndrome (90% to 95% of prostatitis cases).

- TYPE III: A: symptomatic inflammatory prostatitis,
  B: symptomatic non-inflammatory prostatitis.

- No concensus on the causes:
  - residua following bacterial prostatitis,
  - hypoxia,
  - genetic factors,
  - autoimmune disease (TIMUS gland),
  - hormonal disbalance and aging,
  - intraprostatic ductal urine reflux,
  - environmental factors.



EVALUATION OF PATIENT WITH CP/CPPS



Chronic Prostatitis Collaborative Research Network (CPCRN)

THERAPY OF INFLAMMATORY CPSS (TYPE III A)

DRUGS/ PHYSICAL THERAPY	ROUTE/ DURATION/ NOTE
Alpha-adrenoceptor blockers	Oral/ 3-6 months or longer
Empirical administered antibacterial agents (Fluoroquinolones, Co-trimoxazoe, Doxycycline)	Oral/ 2-4 weeks
NSAIDS	Oral/ 1-3 months
Serenoa repens extracts alone or combined with other herbal extracts or supplements (lycopene, selenium, U. dioica, quercetin, cureumin, etc.)	Oral/ 1-3 months
Pygeum Africanum extracts	Oral/ 2 months
Cernitin polle extracts	Oral/ 3 months
Sulbutiamine	Oral/ 4 weeks
Lyophilized bacterial lysate od *Escherichia coli*	Oral/ 3 months
Prostatic massage (weekly)	1-3 months

Magri V, Perletty G et al. Critical issue in chronic prostatitis. Arch Ital Urol Androl 2010;82:75-82.

THERAPY OF NON-INFLAMMATORY CPSS (TYPE III B)

DRUGS/ PHYSICAL THERAPY	ROUTE/ DURATION/ NOTE
Alpha-adrenoceptor blockers	Oral/ 3-6 months or longer
Empirically administered antibacterial agents (Fluoroquinolones, Co-trimoxazoe, Doxycycline)	Oral/ 2 weeks
Low-dose benzodiazepins (diazepam)	Oral/ 3-6 months
Antidepressant drugs (sertralin)	Oral/ 4-8 weeks
5 – alpha – reductase inhibitors	Oral
Bencyclane fumarate	Oral/ 2 months
NSAIDS	Oral/ 2-4 weeks
Behavioral treatments	
Acupuncture	According to specialist`s protocol
Electromagnetic stimulation	According to specialist`s protocol
Heat therapy	According to specialist`s protocol
Prostatic massage (weekly)	1-3 months
Serenoa repens or combined with other herbal extracts	Oral/ 1-3 months
Pygeum Africanum extracts	Oral/ 2 months

Magri V, Perletty G et al. Critical issue in chronic prostatitis. Arch Ital Urol Androl 2010;82:75-82.

ANTIMICROBIAL THERAPY FOR CPPS !!??

- **Still most common therapy for chronic prostatitis despite RCTs!**

WHY?

- **Belief that all prostatitis is due to infection:**
  - **difficult to culture bacteria and biofilm disease.**

HOW MIGHT ANTIBIOTICS HELP CPPS?

- **Antibiotics have direct anti-inflammatory effects:**
  - **quinolones, macrolides and tetracyclines block IL-6 and IL-8.**
- **Intracellular pathogens often not detected (Chlamydia).**
- **Placebo effect.**

MANAGEMENT OF CHRONIC PROSTATITIS/ CHRONIC PELVIC PAIN SYNDROME: AN EVIDENCE-BASED APPROACH

JORDAN D. DIMITRAKOV, STEVEN A. KAPLAN, KURT KROENKE, JEFFREY L. JACKSON, AND MICHAEL R. FREEMAN

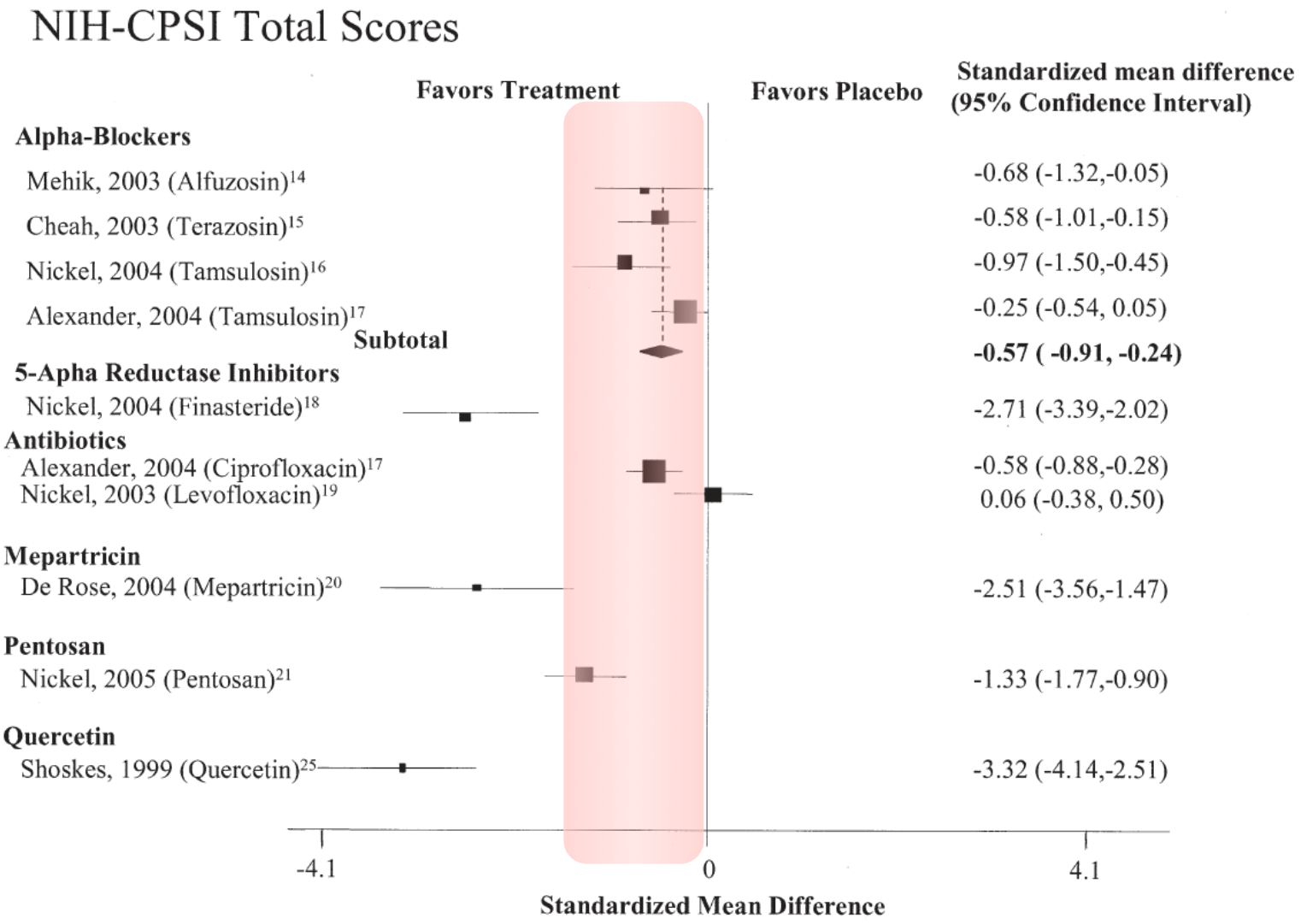


FIGURE 1. *Relative risk of overall improvement.*

Management of Chronic Prostatitis/ Chronic Pelvic Pain Syndrome

A Systematic Review and Network Meta-analysis

JAMA, January 5, 2011—Vol 305, No. 1

Nickel JC et al.

- **23 of 262 studies (1974 - 2010).**
- **a-Blockers, antibiotics, and combinations of these therapies appear to achieve the greatest improvement in clinical symptom scores compared with placebo.**
- **Antiinflammatory therapies, phytotherapies and finasteride have a much lesser but somewhat measurable benefit.**
- **No reliable treatment has been identified!**

Guidelines on Urological Infections

M. Grabe (chairman), T.E. Bjerklund-Johansen, H. Botto, B. Wullt, M. Çek, K.G. Naber, R.S. Pickard, P. Tenke, F. Wagenlehner

Despite the existence of some scientifically valid studies, no specific recommendations have been made for treatment of patients with CPPS until now!

European Association of Urology

ASYMPTOMATIC INFLAMMATORY PROSTATITIS (TYPE IV) – CLINICAL SIGNIFICANCE?

- **It is still unrecognized and it is often left untreated.**

- **Prevalence: - 95 % of tissue samples after TURP** (Blumenfeld, 1992),
  - 97% of tissue samples after biopsy (Nadler, 1995).

TYPE IV PROSTATITIS AND PROSTATE CANCER DETECTION?

- **Acute prostatitis contributes to the lack of PSA specificity!**

- **What about chronic hystological inflammation?**

- **Should we treat patients with asymptomatic prostatitis?**

PROSTATITIS AND PSA – PATHOPHYSIOLOGY

PROSTATITS - INFLAMMATION

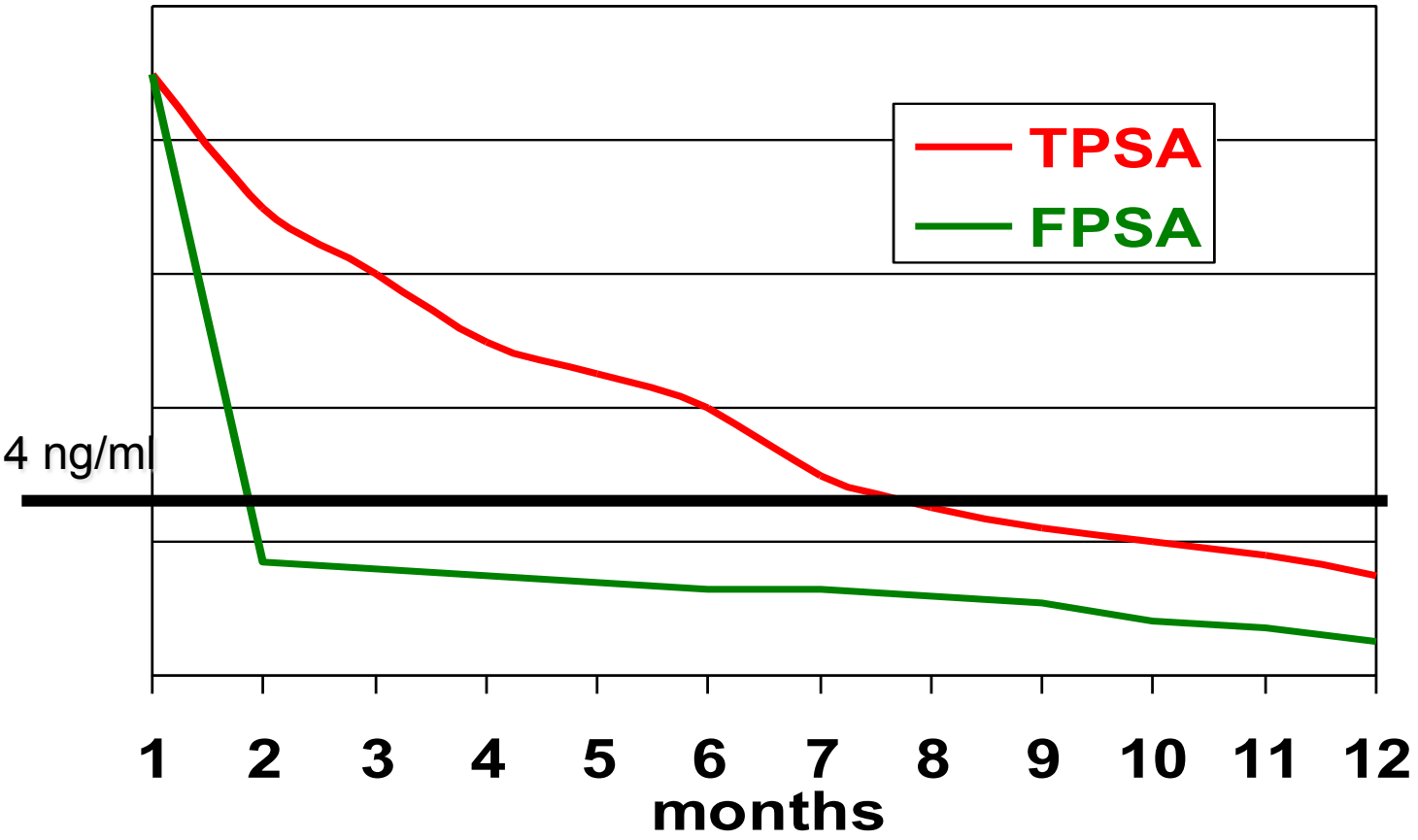
EPITHELIAL CELL AND BASAL MEMBRANE DESTRUCTION, INCREASED PERMEABILITY

PSA LEAKAGE

TYPE IV PROSTATITIS AND PSA?

AUTHOR	SPECIMENS	INFLAMMATION GRADING GROUPS	TPSA	FPSA
Ornstein	PROSTATE BIOPSY	Acute Chronic	0 0	- 0
Morote	PROSTATE BIOPSY	Acute Chronic	0 0	+ 0
Scatonni	OPEN PROSTATECTOMY	Acute Chronic	0 0	+ 0
Meyer	BIOPSY, TURP,OP	Asymptomatic prostatitis, BPH, CaP	+	-
Stancik	PROSTATE BIOPSY	Asymptomatic prostatitis, BPH, CaP	+	-
Minardi	BIOPSY, TURP,OP	Asymptomatic prostatitis, BPH, CaP	+	-
Jung	PROSTATE BIOPSY	Asymptomatic prostatitis, BPH, CaP	+	-
Rowe	PROSTATE BIOPSY	Asymptomatic prostatitis, BPH, CaP	0	-

PROSTATITIS AND PSA VALUES TIMELINE



TPSA $^{T1/2}$ > FPSA $^{T1/2}$

ACUTE INFECTION → **CHRONIC INFECTION**

Zackrisson, Urology, 2003.

ASYMPTOMATIC PROSTATITIS THERAPY AND PSA

AUTHOR	THERAPY (min. 4 weeks)	TPSA	FPSA	PSA DECREASED
Bozeman (J Urol, 2002)	quinolones, SMX/TMP, NSAR	decreased	not analised	**36%**
Lorente (Int J Biol Markers, 2003)	quinolones, SMX/TMP, tetracyclines	decreased	elevation	**20 %**
Zackrisson (Urology, 2003)	quinolones, SMX/TMP	decreased	elevation	**30 %**
Potts (J Urol, 2000)	quinolones, SMX/TMP	decreased	not analised	**20 %**

ASYMPTOMATIC PROSTATITIS TREATMENT AND PROSTATE CANCER SCREENING?!

PRO:

- INCREASING PSA SPECIFICITY AND SENSITIVITY.
- DECRESING RATE OF REPEAT BIOPSIES.
- OVERDIAGNOSIS REDUCTION.

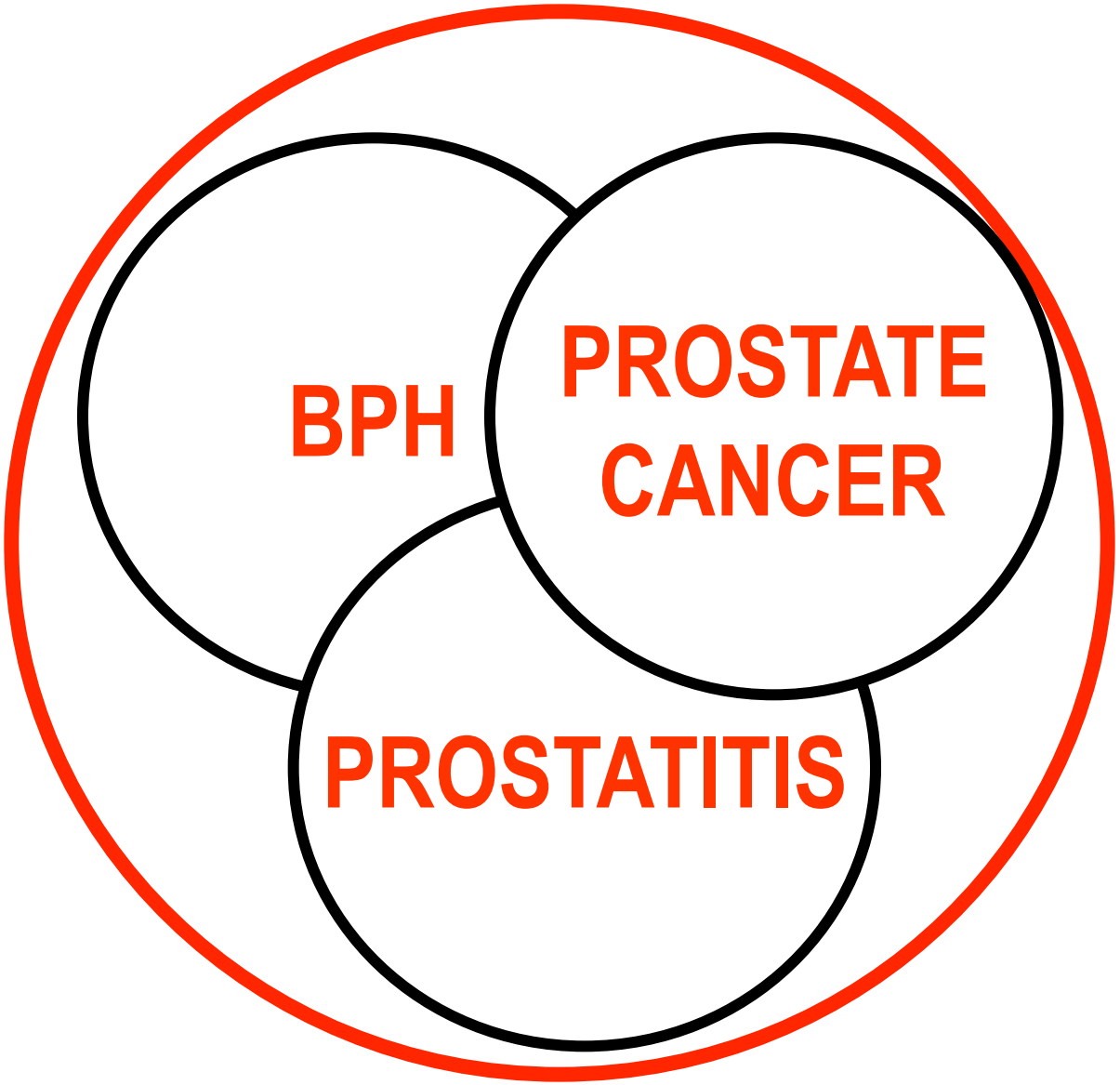
CONTRA:

- ASYMPTOMATIC PROSTATITIS SCREENING?
- SHOULD WE TREAT HISTOLOGICAL FINDING?
- UROPATHOGEN IS ISOLATED IN LESS THAN 10%.
- EMERGING EXPENCES?

CHRONIC PROSTATITIS – OPEN QUESTIONS?

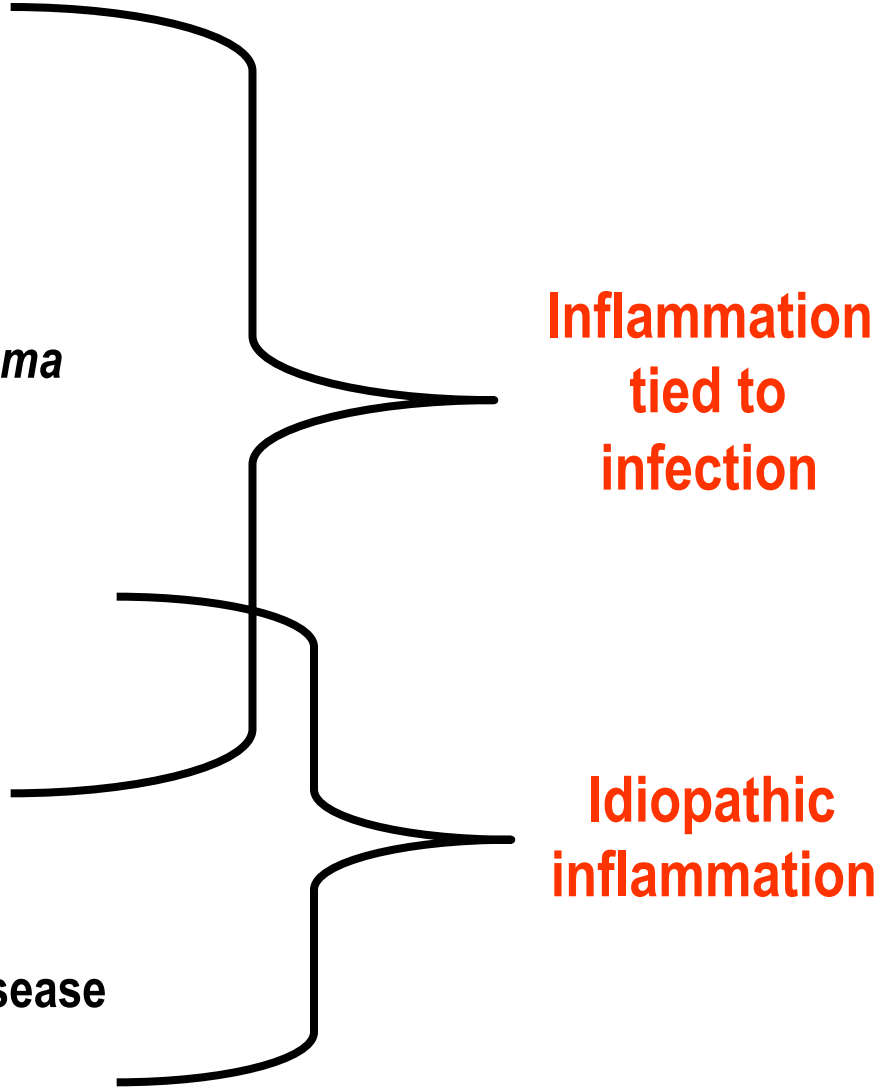
- Treatment – for how long?
- Which is the correct test for CBP – 2 or 4 glass test?
- The role of gramm(+) and nontraditional pathogens in CBP?
- No concensus on the causes of CP/CPPS?
- Is there a rationale for antimicrobial therapy for type IIII and type IV prostatitis?

COMMON SYMPTOMS, ETIOLOGY, PATHOGENESIS?

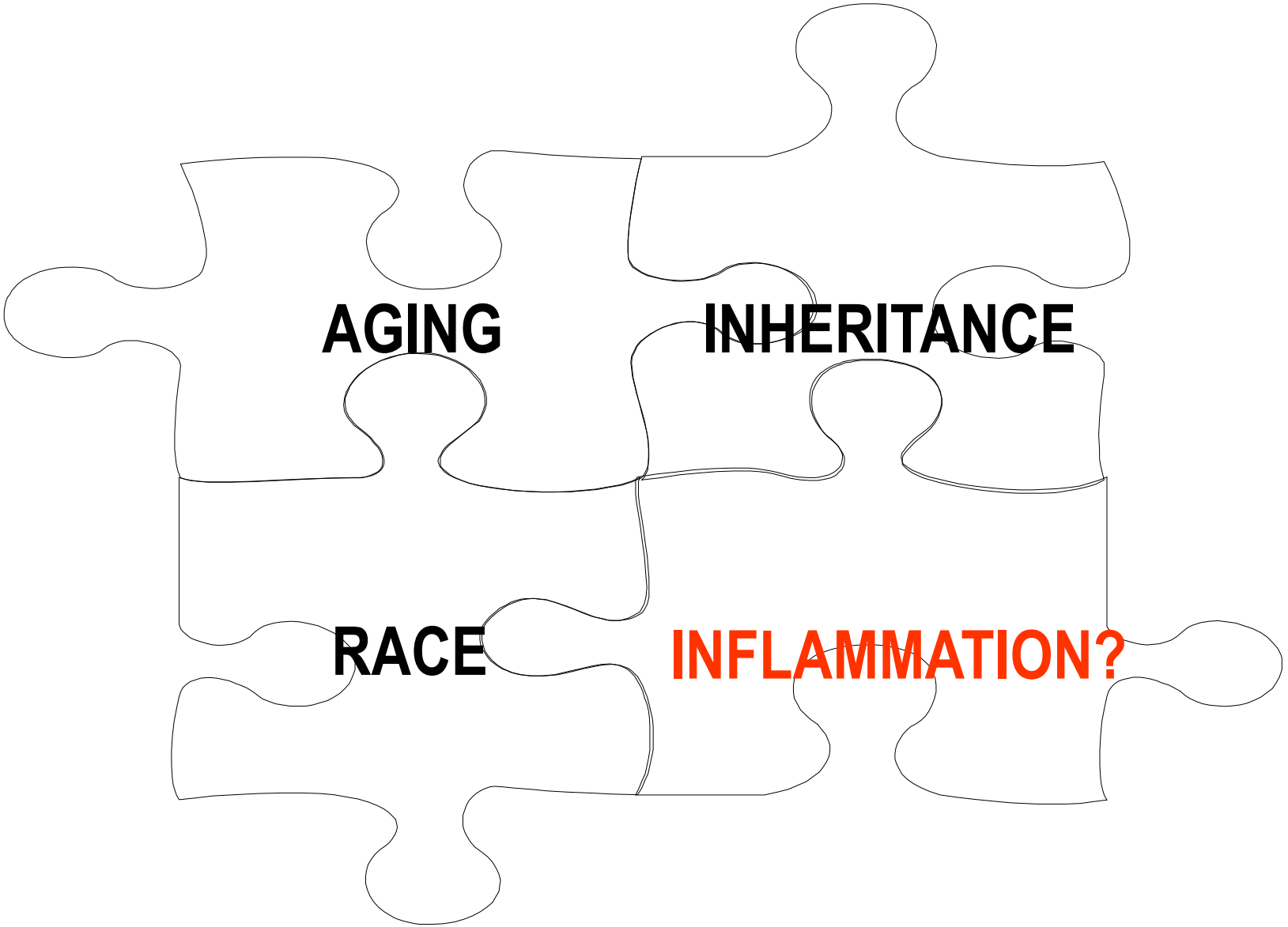


INFLAMMATION/INFECTION AND CANCERS?

- GASTRIC CANCER – *H. pylori*
- LIVER CANCER – *HBV, HCV*
- GALLBLADDER CANCER – *Schistosoma*
- UTERINE/CERVICAL CANCER - *HPV*
- PROSTATE CANCER
- LUNG CANCER
- COLONIC CANCER – inflammatory disease

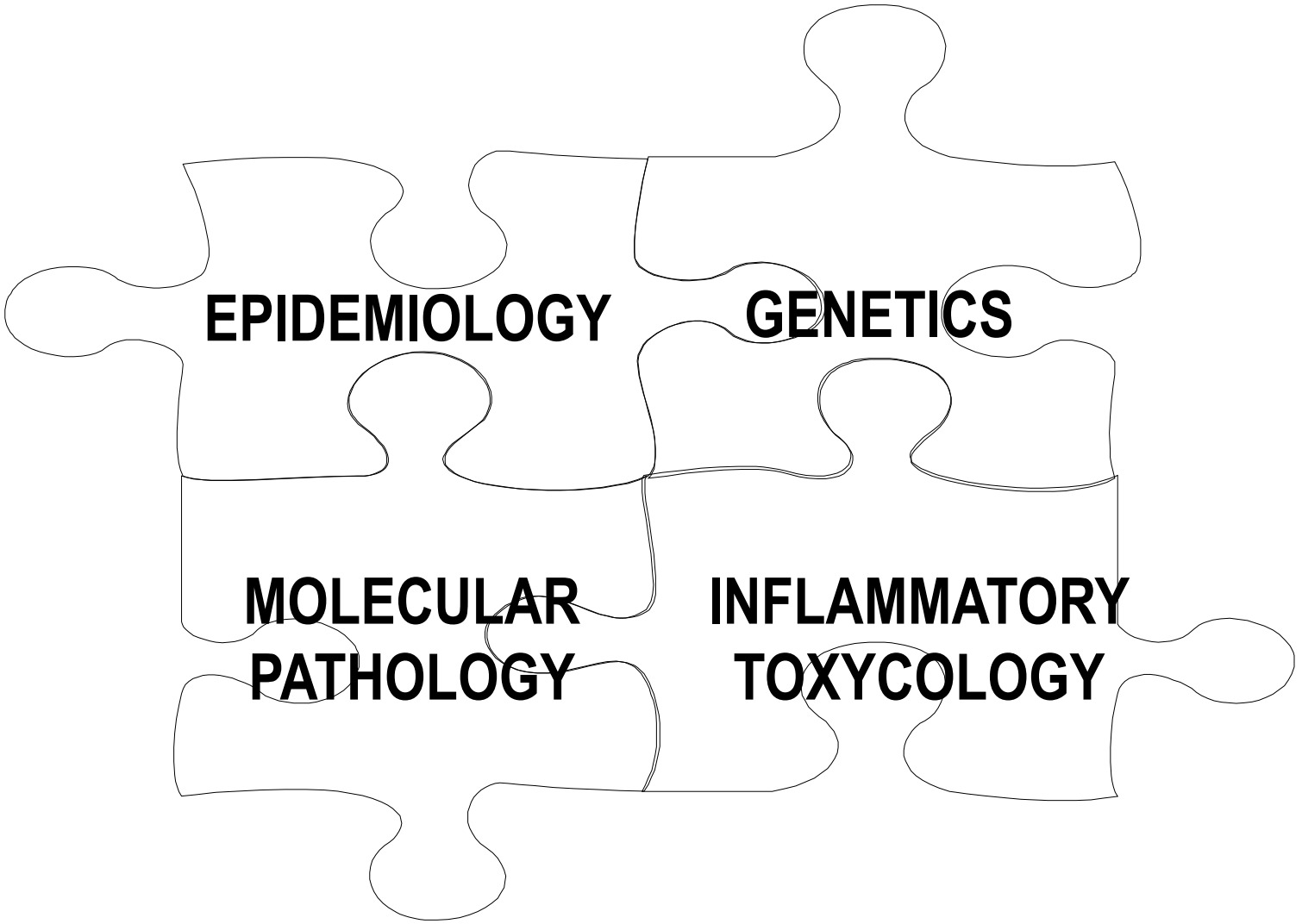


PROSTATE CANCER RISK FACTORS



INFLAMMATION/INFECTION AND PROSTATE CANCER ?!

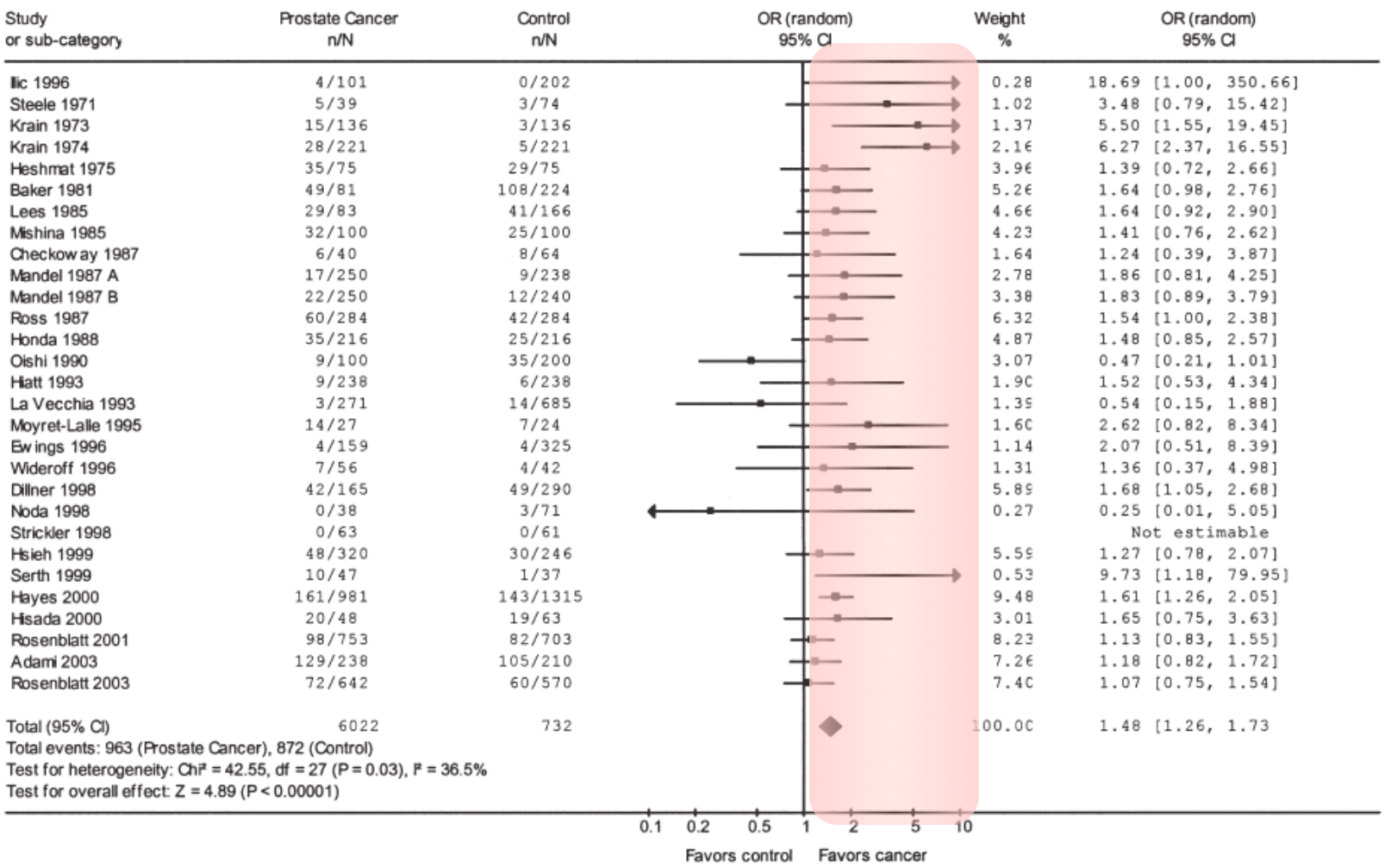
THE BEGINING: Ravich,A. and Ravich,R.A. (1951) Prophylaxis of cancer of the prostate, penis and cervix by circumcision. *N. Y. State J. Med.*, **51**, 1519–1520.



Prostate Cancer and Sexually Transmitted Diseases: A Meta-analysis

Marcia L. Taylor, MD; Arch G. Mainous, III, PhD; Brian J. Wells, MD, MS

Review: Prostate Cancer and STD
Comparison: 01 Prostate Cancer and any STD
Outcome: 01 Prostate Cancer and any STD



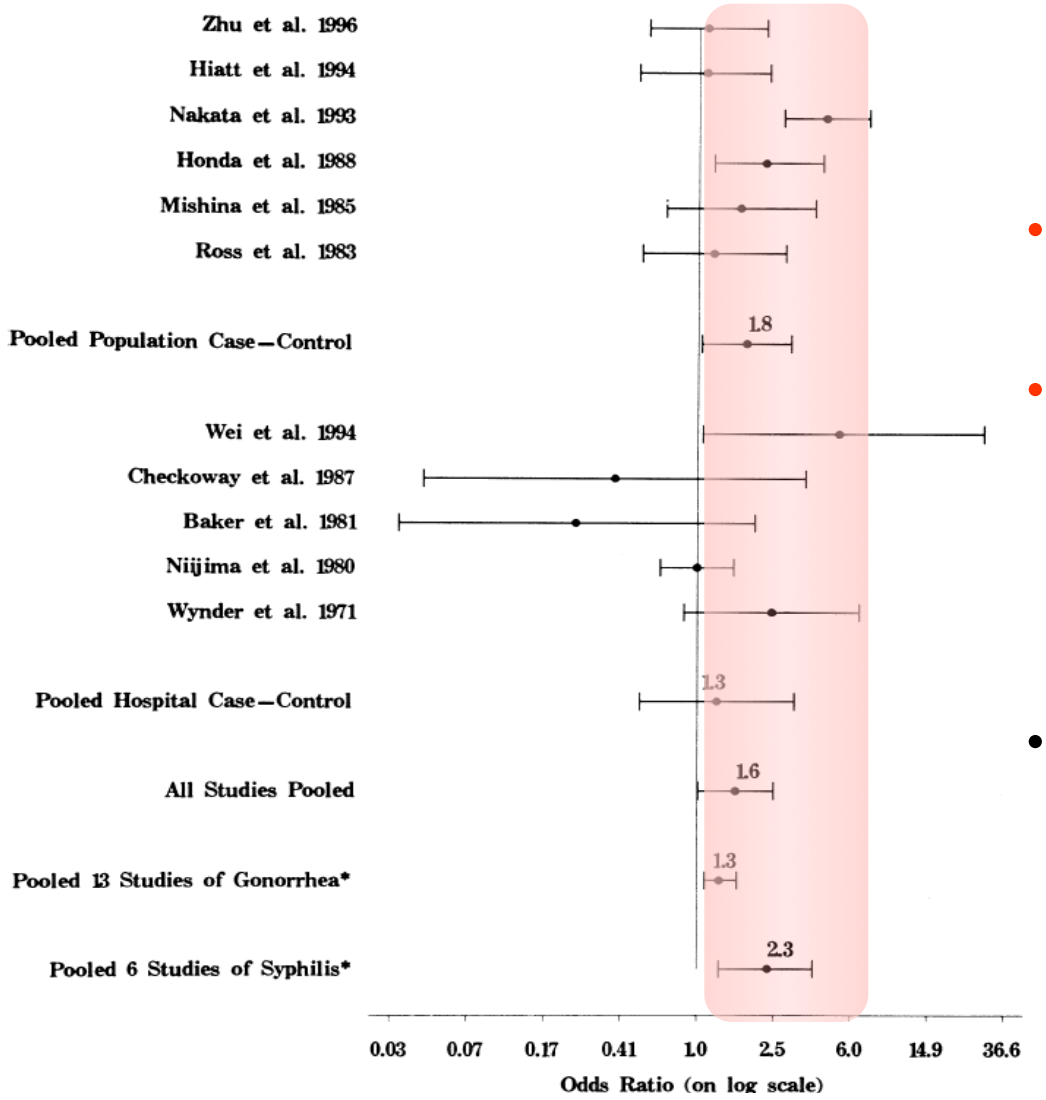
Study or sub-category	Prostate Cancer n/N	Control n/N	Weight %	OR (random) 95% CI
Ilic 1996	4/101	0/202	0.28	18.69 [1.00, 350.66]
Steele 1971	5/39	3/74	1.02	3.48 [0.79, 15.42]
Krain 1973	15/136	3/136	1.37	5.50 [1.55, 19.45]
Krain 1974	28/221	5/221	2.16	6.27 [2.37, 16.55]
Heshmat 1975	35/75	29/75	3.96	1.39 [0.72, 2.66]
Baker 1981	49/81	108/224	5.26	1.64 [0.98, 2.76]
Lees 1985	29/83	41/166	4.66	1.64 [0.92, 2.90]
Mishina 1985	32/100	25/100	4.23	1.41 [0.76, 2.62]
Checkoway 1987	6/40	8/64	1.64	1.24 [0.39, 3.87]
Mandel 1987 A	17/250	9/238	2.78	1.86 [0.81, 4.25]
Mandel 1987 B	22/250	12/240	3.38	1.83 [0.89, 3.79]
Ross 1987	60/284	42/284	6.32	1.54 [1.00, 2.38]
Honda 1988	35/216	25/216	4.87	1.48 [0.85, 2.57]
Oishi 1990	9/100	35/200	3.07	0.47 [0.21, 1.01]
Hiatt 1993	9/238	6/238	1.90	1.52 [0.53, 4.34]
La Vecchia 1993	3/271	14/685	1.39	0.54 [0.15, 1.88]
Moyret-Lalle 1995	14/27	7/24	1.60	2.62 [0.82, 8.34]
Ewings 1996	4/159	4/325	1.14	2.07 [0.51, 8.39]
Wideroff 1996	7/56	4/42	1.31	1.36 [0.37, 4.98]
Dillner 1998	42/165	49/290	5.89	1.68 [1.05, 2.68]
Noda 1998	0/38	3/71	0.27	0.25 [0.01, 5.05]
Strickler 1998	0/63	0/61		Not estimable
Hsieh 1999	48/320	30/246	5.59	1.27 [0.78, 2.07]
Serth 1999	10/47	1/37	0.53	9.73 [1.18, 79.95]
Hayes 2000	161/981	143/1315	9.48	1.61 [1.26, 2.05]
Hisada 2000	20/48	19/63	3.01	1.65 [0.75, 3.63]
Rosenblatt 2001	98/753	82/703	8.23	1.13 [0.83, 1.55]
Adami 2003	129/238	105/210	7.26	1.18 [0.82, 1.72]
Rosenblatt 2003	72/642	60/570	7.40	1.07 [0.75, 1.54]
Total (95% CI)	6022	732	100.00	1.48 [1.26, 1.73]

Total events: 963 (Prostate Cancer), 872 (Control)
Test for heterogeneity: $Chi^2 = 42.55$, df = 27 (P = 0.03), $I^2 = 36.5\%$
Test for overall effect: Z = 4.89 (P < 0.00001)

UROLOGY 60 (1), 2002

EPIDEMIOLOGIC ASSOCIATION BETWEEN PROSTATITIS AND PROSTATE CANCER

LESLIE K. DENNIS, CHARLES F. LYNCH, AND JAMES C. TORNER



- increased risk in men with history of prostatitis
- increased risk in men treated for syphilis and gonorrhoea

BIAS:

- men with prostatitis are more likely to be screened for prostate cancer!?

OPEN ACCESS Freely available online

PLoS one

Prostatitis, Sexually Transmitted Diseases, and Prostate Cancer: The California Men's Health Study

Iona Cheng[1]*, John S. Witte[2], Steven J. Jacobsen[3], Reina Haque[3], Virginia P. Quinn[3], Charles P. Quesenberry[4], Bette J. Caan[4], Stephen K. Van Den Eeden[4]

January 2010 | Volume 5 | Issue 1

- study design: 68 675 men, follow-up, prospective, 1 658 cancers
- men having a history of prostatitis had an increased risk of cancer!
- longer duration of prostatitis symptoms was also associated with an increased risk of prostate cancer!
- STDs were not associated with overall prostate cancer risk!

Carcinogenesis vol.26 no.7 pp.1170–1181, 2004
doi:10.1093/carcin/bgh317
Advance Access publication October 21, 2004

Ganesh S.Palapattu[1], Siobhan Sutcliffe[2], Patrick J.Bastian[1], Elizabeth A.Platz[1,2], Angelo M.De Marzo[1,3,4], William B.Isaacs[1,3] and William G.Nelson[1,3,4,*]

REVIEW

Prostate carcinogenesis and inflammation: emerging insights

Table II. Sexually transmitted infections and prostate cancer

Infection	Assay	Findings
Human papillomas virus 16	Serology	+/−
	In situ hybridization and PCR	+/−
Human papillomas virus 18	Serology	+
Human papillomas virus 33	Serology	None
Human papillomas virus 11	Serology	None
Chlamydia trachomatis	Serology	None
Syphilis	Serology	+/−
Herpes simplex virus 2	Serology	+/−
	Immunofluorescent staining, *in situ* hybridization	None
Human herpes virus 8	Serology	+/−
Cytomegalovirus	Immunohistochemistry, PCR, *in situ* hybridization	+[a]
Epstein–Barr virus	Immunohistochemistry, PCR	+[a]

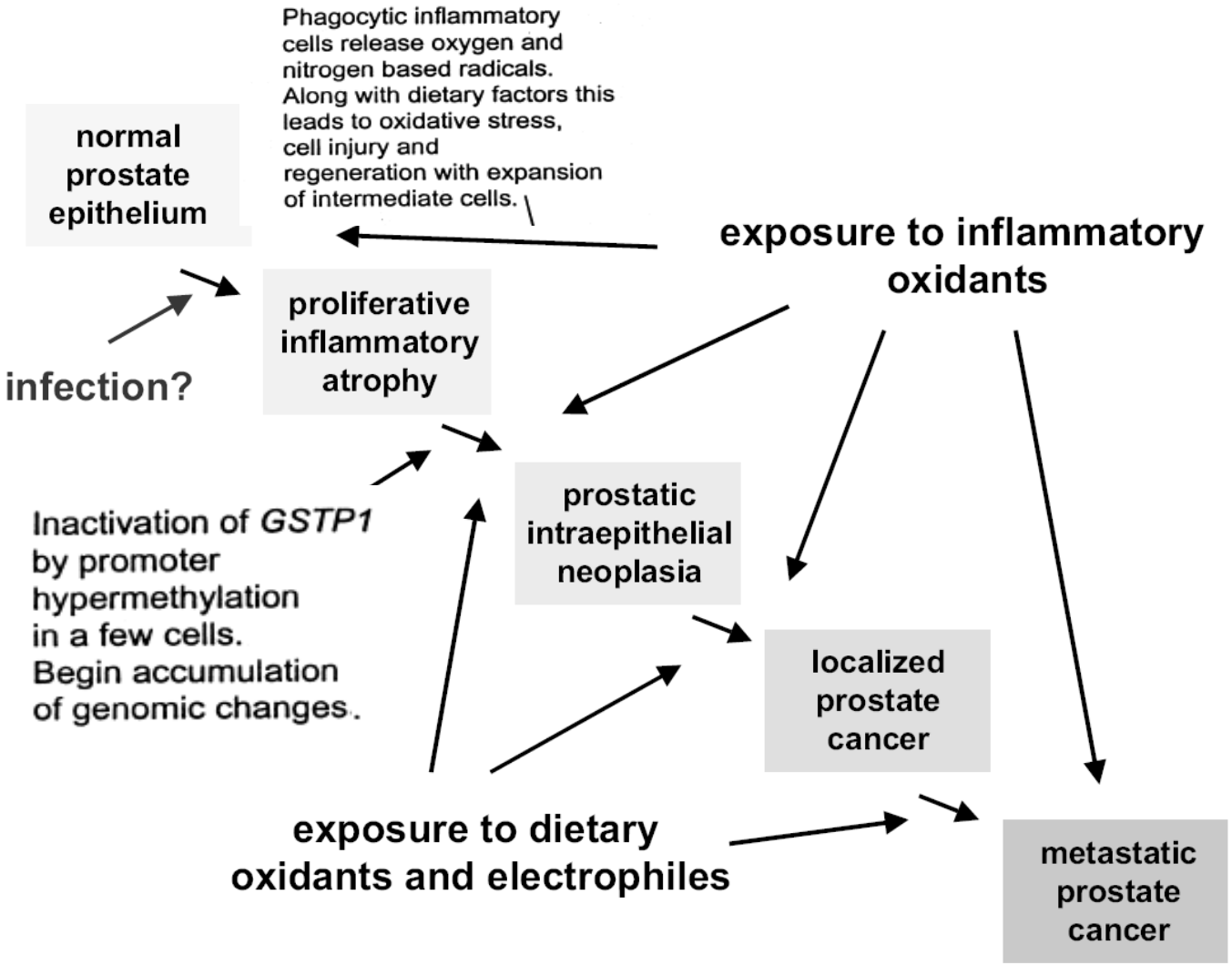
PATHOGENS ISOLATED FROM PROSTATIC TISSUE

- VIRUSES
  - HPV (16 and 18)
  - HSV (1, 2, 8, EBV)
  - Polyoma (JC, BK)
  - XMLRV (Klein et al, Curr Opin Urol, 2008):
    - found in 27% of prostate cancers,
    - linked to more aggressive tumors.
- BACTERIA
  - Chlamydia, E. coli, Staph., Strep., Corynebact.,Entero., Peptostrep., Aeromonas,...
- OTHER
  - Ureaplasma
  - T. vaginalis

UROLOGY 57 (Supplement 4A), April 2001

NEW CONCEPTS IN THE PATHOLOGY OF PROSTATIC EPITHELIAL CARCINOGENESIS

ANGELO M. DE MARZO, MATHEW J. PUTZI, AND WILLIAM G. NELSON



GENETIC SUSCEPTIBILITY AND OXIDATIVE STRESS IN PROSTATE CANCER: INTEGRATED MODEL WITH IMPLICATIONS FOR PREVENTION

ERIC A. KLEIN, GRAHAM CASEY, AND ROBERT SILVERMAN

UROLOGY 68 (6), 2006

TABLE II. ***Prostate cancer susceptibility genes***

Gene	Chromosomal Location*	Year Identified	Function
ELAC2/HPC2	17p11	2001	Unknown
RNASEL/HPC1	1q24-25	2002	Apoptosis and susceptibility to infection
SR-A/MSR1	8p22-23	2002	Inflammation and susceptibility to infection
OGG1	3p26.2	2002	DNA repair of oxidative damage
CHEK2	22q12.1	2003	DNA damage signaling and cell cycle control
BRCA2	13q12.3	2003	DNA repair
PON1	7q21.3	2003	Antioxidant/free radical scavenger
MIC-1	19p13	2004	Modulation of inflammation
TLR4	9q32-33	2004	Susceptibility to infection

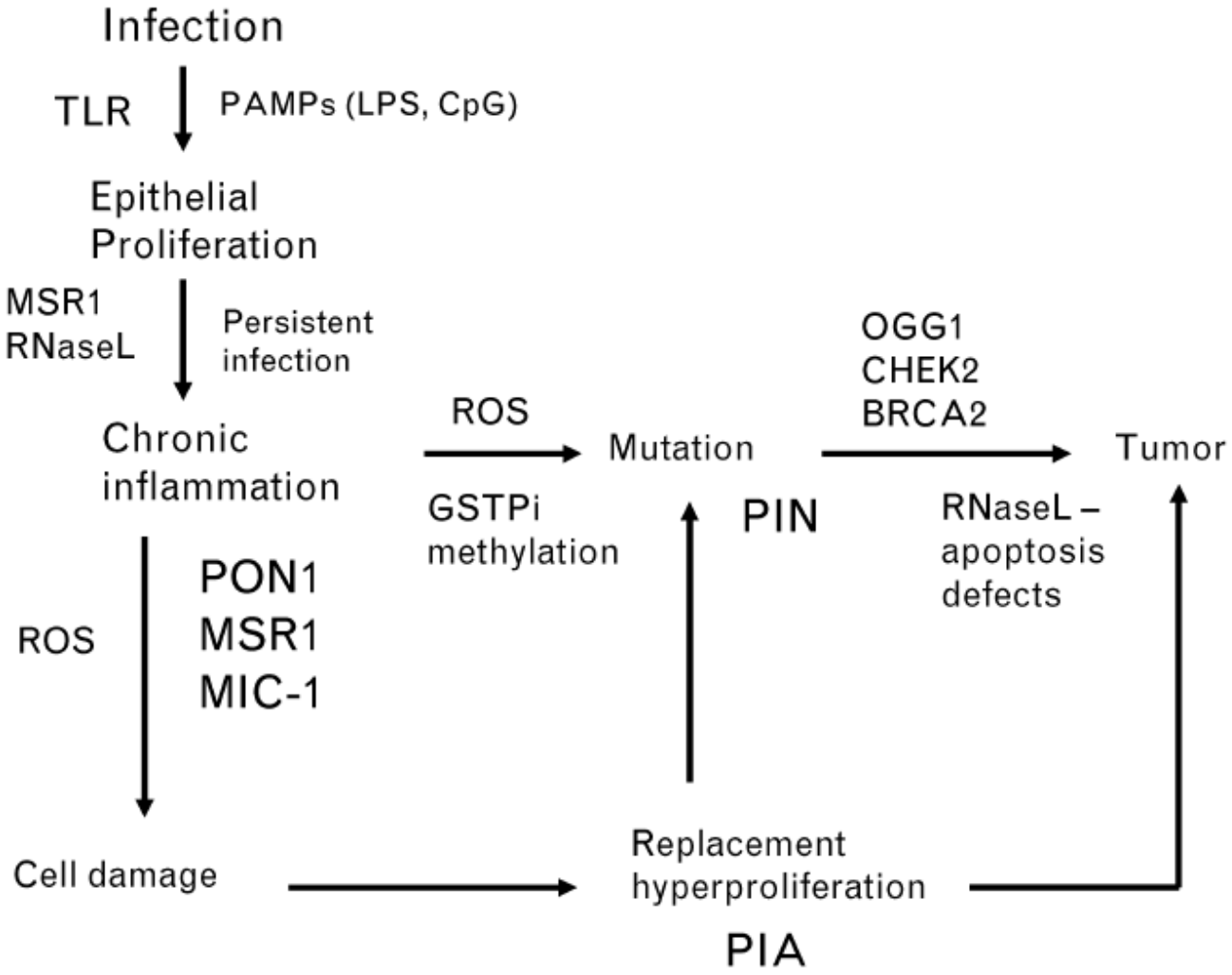
* *Source: Online Mendelian Inheritance in Man; available at: http://www.ncbi.nlm.nih.gov.*

Current Opinion in Urology 2008, 18:315–319

Inflammation, infection, and prostate cancer

Eric A. Klein[a,c,d] and Robert Silverman[b,c,d]

[a]Glickman Urologic and Kidney Institute, Cleveland, [b]Department of Cancer Biology, Lerner Research Institute, Cleveland, [c]Taussig Cancer Institute, Cleveland and [d]Cleveland Clinic Lerner College of Medicine, Cleveland Clinic, Cleveland, Ohio, USA



Carcinogenesis vol.26 no.7 pp.1170–1181, 2004
doi:10.1093/carcin/bgh317
Advance Access publication October 21, 2004

REVIEW

Ganesh S.Palapattu[1], Siobhan Sutcliffe[2], Patrick J.Bastian[1], Elizabeth A.Platz[1,2], Angelo M.De Marzo[1,3,4], William B.Isaacs[1,3] and William G.Nelson[1,3,4,*]

Prostate carcinogenesis and inflammation: emerging insights

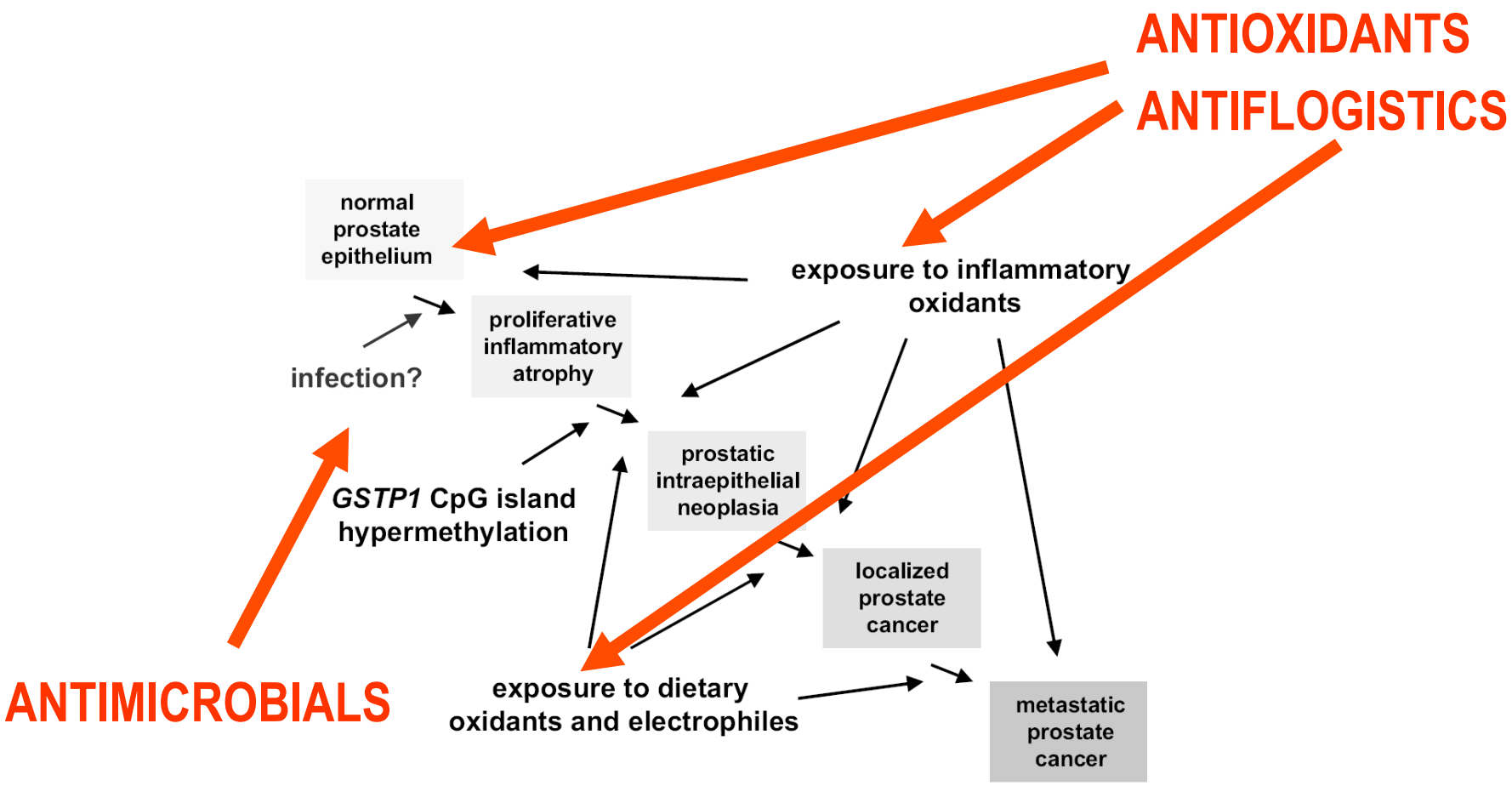
NEW PARADIGM FOR MOLECULAR PATHOGENESIS OF PROSTATE CANCER

CHRONIC INFLAMMATORY RESPONSE

OXYDATIVE DAMAGE, ALTERATION OR MUTATION OF GENES REGULATING CELL DEATH/APOPTOSIS AND REGENERATION

PROSTATE CANCER

TREATING PROSTATITIS – PREVENTING PROSTATE CANCER?



TAKE HOME MESSAGES!

- 3 A's of chronic prostatitis medical therapy (Nickel, 2006):
  - Antibiotics have definite role for category II chronic prostatitis, many patients with category III will respond but mechanism unclear.
  - α-1 blockers and antiinflammatory agents can relieve symptoms!
- First line treatment: QUINOLONES: duration of therapy – 4 wks (6-12)!
- Bacteriologic cure is not always equivalent to cure!
- Think about "unusual", "non-traditional uropathogens" but:
  - the problem of urethral harborment versus infection of the prostate cannot be solved by localization tests!
- Use 4-glass test for proper diagnosis, 2-glass test for follow up!

TAKE HOME MESSAGES!

A NEW RATIONALE FOR ASYMPTOMATIC PROSTATITIS MANAGEMENT!

- Treatment of prostatitis is increasing PSA specificity and sensitivity for prostate cancer screening!
- Chronic (long lasting) inflammation may play an important role in prostate carcinogenesis!
- Prevention of prostate cancer most likely feasible (by prevention, early diagnosis and treatment of prostatitis and STDs):
  - anti-inflammatory drugs,
  - anti-oxidants (nutrition),
  - antibiotics!

BEST, MOST CONCISE REFERENCES

- Škerk,V et al. Azithromycin: 4.5- or 6.0-gram dose in the treatment of patients with chronic prostatitis caused by Chlamydia trachomatis--a randomized study. J Chemother 2004; 16: 408-10.
- Dimitrakov JD, et al. Management of chronic prostatitis/ chronic pelvic pain syndrome: an evidence-based approach. Urology. 2006 May;67(5):881-8.
- De Marzo AM et al. Inflammation in prostate carcinogenesis. Nat Rev Cancer. 2007 Apr;7(4): 256-69.
- Magri V, Perletty G. Critical issue in chronic prostatitis. Arch Ital Urol Androl 2010;82:75-82.
- Murphy AB, Nadler RB. Pharmacotherapy strategies in chronic prostatitis/chronic pelvic pain syndrome management. Expert Opin Pharmacother. 2010 Jun;11(8):1255-61.
- Nickel JC et al. Management of chronic prostatitis/chronic pelvic pain syndrome: a systematic review and network meta-analysis. JAMA. 2011 Jan 5;305(1):78-86.