

Fluctuations in PSA and Use of Antibiotics

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Normal Variability of PSA

- Anticipated since concentration in prostatic fluid approximately a million-fold higher than in serum
- Fluctuations in serum may not necessarily represent the same degree of fluctuation in prostatic fluid
- Etiology:
 - Analytic
 - Biologic

Natural Variability of PSA

- Analytic
 - Assay standardization and performance
 - Sample handling and laboratory processing can lead to intra-assay variation
 - Timing of measurements
 - Dependent on PSA heterogeneity

Assay standardization bias

- Multiple studies demonstrate discrepancies in PSA measurements between different detection assays (Nixon RG, J Urol 1998; Link RE, J Urol 2004; Stephan C, Clin Chem 2006)
- Two commercially available PSA assays prospectively compared in 103 men undergoing CaP screening
- Concordance index between 2 assays = 0.74
- 73 biopsies were performed
 - 16 prostate cancer cases were detected

Assay standardization bias

Assay	Men with free/total ratio $\leq 20\%$ (cutoff for biopsy)	Prostate Cancer Sensitivity	Prostate Cancer Specificity
AxSYM*	51%	63	94
Immulite	70%	25	4

$p < 0.0001$

* (\uparrow fPSA)

tPSA $\Delta = 0.12$

fPSA $\Delta = 0.17$

3.2% Δ in F/T PSA

Sotelo, RJ et al. Urology 69(6): 1143-6, 2007

Assay standardization bias: comparison of five assays

- 314 patients with prostate cancer, 282 with no evidence of malignancy
- Interchangeability of total, free, and %free PSA was inadequate between commercial PSA assays

Assay standardization bias: comparison of five assays

	100%	87%	87%	115%	87%
	Access	AxSYM	Centaur	Immulite	Elecsys
tPSA					
NPCa >4 $\mu\text{g/L}$, ^b n	139	117	120	144	139
PCa <4 $\mu\text{g/L}$, ^c n	68	86	93	46	59
Cutoff at 90% sensitivity, $\mu\text{g/L}$	2.82 (2.40–3.40)	2.60 (2.12–3.04)	2.52 (2.12–3.07)	3.12 (2.68–3.75)	3.02 (2.48–3.54)
Cutoff at 90% specificity, $\mu\text{g/L}$	7.68 (7.21–8.21)	6.71 (6.20–7.05)	6.67 (6.26–7.32)	8.70 (8.33–9.15)	8.04 (7.38–8.60)
Area under the ROC curve	0.70 (0.66–0.74)	0.72 (0.68–0.75)	0.71 (0.67–0.75)	0.71 (0.68–0.75)	0.70 (0.66–0.74)
%fPSA					
Cutoff at 90% sensitivity, %	18.7 (17.2–20.0)	24.2 (22.0–25.7)	24.1 ^d (21.8–25.8)	15.4 (14.5–17.1)	17.8 (17.0–19.1)
Cutoff at 90% specificity, %	10.2 (9.39–11.7)	12.8 (11.5–14.2)	9.94 (8.73–12.9)	8.50 (7.53–9.35)	9.94 (8.80–10.7)
Area under the ROC curve ^e	0.81 (0.78–0.84)	0.80 (0.77–0.83)	0.77 (0.74–0.81)	0.81 (0.77–0.84)	0.79 (0.75–0.82)

^a Values in parentheses are 95% confidence intervals.

^b Number of the 282 NPCa patients with tPSA values above the conventional threshold of 4 $\mu\text{g/L}$.

^c Number of the 314 PCa patients with tPSA values below the conventional threshold of 4 $\mu\text{g/L}$.

^d The cPSA values transformed into fPSA concentrations by use of the equation $\text{fPSA} = \text{tPSA} - \text{cPSA}$ were used to calculate %fPSA values.

^e Only the area obtained with the ADVIA Centaur assay was significantly different from the Access Hybritech value (pairwise comparison, $P = 0.006$).

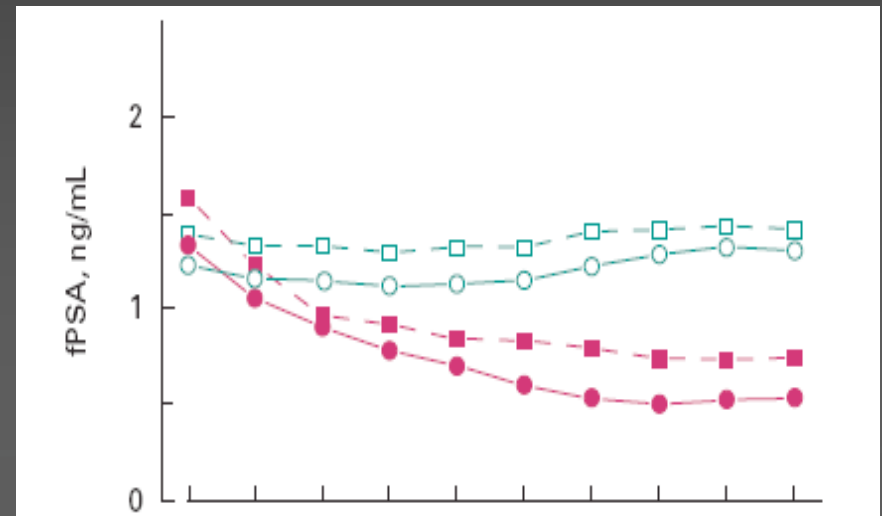
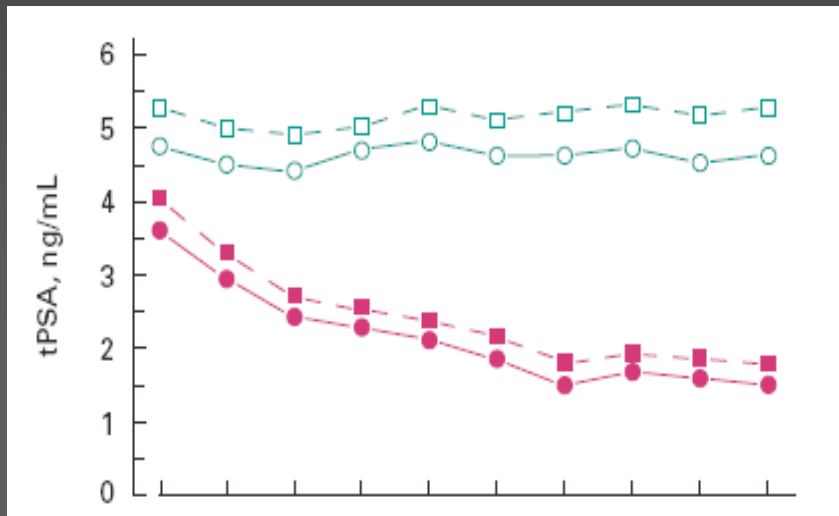
Natural Variability of PSA

- Biologic
 - Any process which alters prostatic acini basement membrane integrity, i.e. prostatic inflammation, BPH, ejaculation, prostate manipulation
 - 5α -reductase inhibitors and other hormone manipulating drugs/processes
 - PSA metabolism ($t_{1/2} = 2-3$ days)
 - Age
 - Seasons, exposure to sunlight

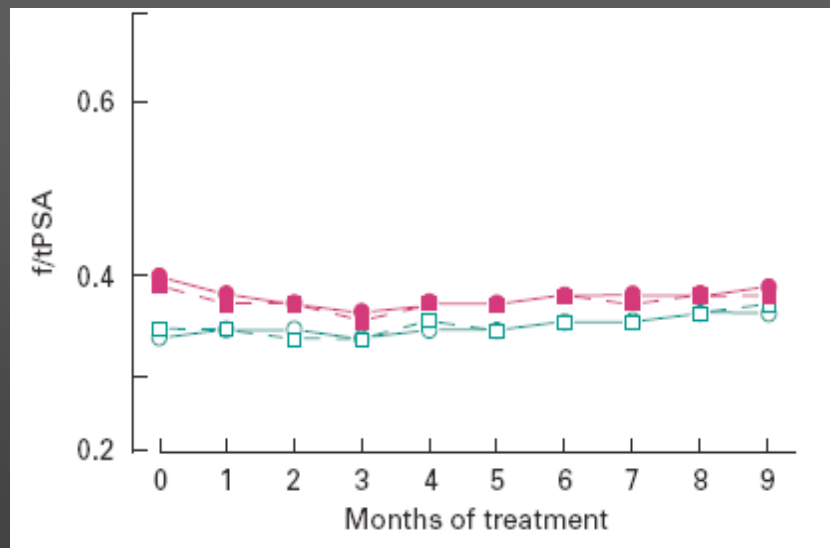
Finasteride: proportional reduction on PSA forms

- 40 patients with BPH randomized to finasteride (n=30) or placebo (n=10)
 - Follow-up: 9 months
 - Treatment group: Both total and free PSA significantly decreased by approximately $\frac{1}{2}$ (constant fPSA : tPSA ratio)
 - Control group: no significant change
 - Suggestion: decrease in free: total ratio could potentially be of neoplastic origin rather than a consequence of finasteride therapy

Finasteride: proportional reduction on PSA forms



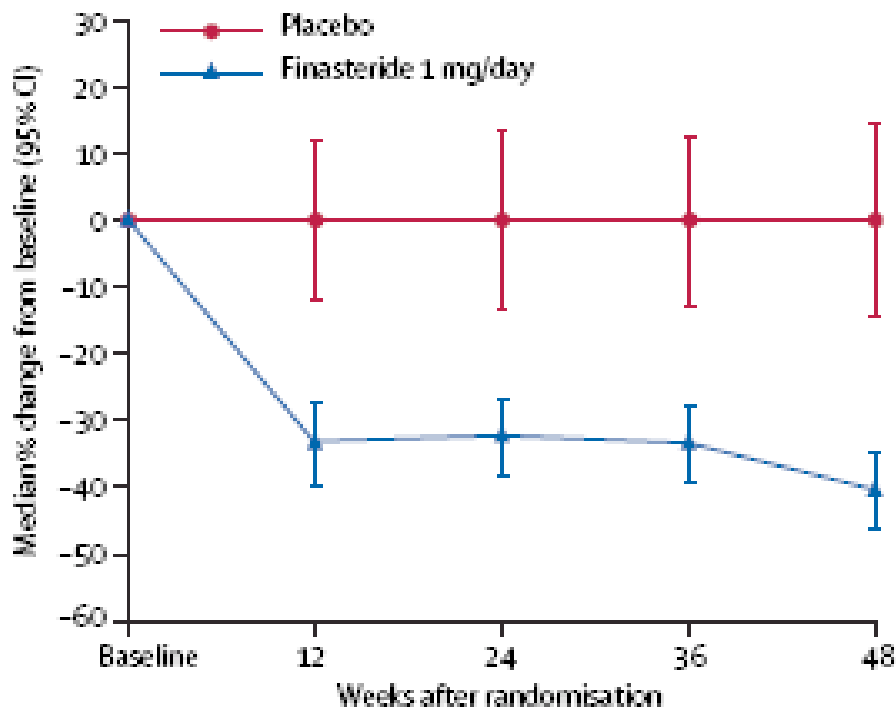
○ = plasma
 □ = serum
 red = finasteride
 green = placebo



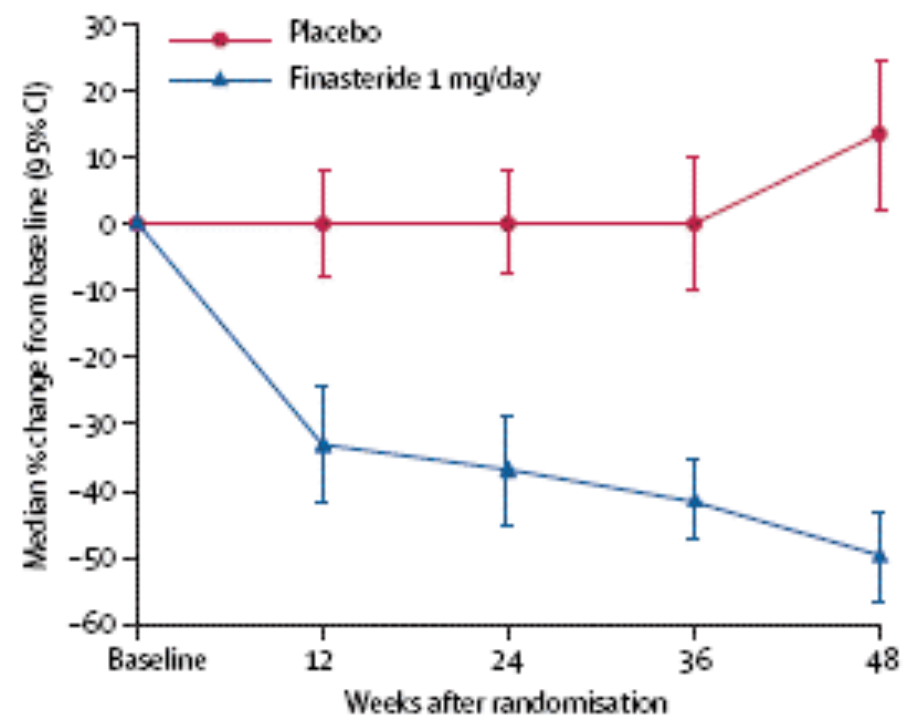
5 mg/day finasteride halves PSA levels by 12 months, does a 1mg daily dose?

- Randomized, controlled trial evaluating effect of 1 mg/day finasteride (Propecia[®]) on PSA levels in 355 men with male-pattern hair loss
 - Follow-up at 48 weeks
 - Men stratified by age
 - Ages 40-49
 - Ages 50-59

5 mg/day finasteride halves PSA levels by 12 months, does a 1mg daily dose?



Men ages 40-49
40% (95% CI 34-46) median decrease



Men ages 50-59
50% (95% CI 44-57) median decrease

Herbal supplements

- Multiple studies show no effect of saw palmetto (*Serenoa repens*) on PSA levels
 - *In vitro* prostate cancer cell lines treated with saw palmetto fruit extract (Permixon[®]) reveal no suppression of the androgen receptor and maintenance of PSA protein expression, unlike lines treated with finasteride

Double-blind, randomized multicenter study comparing Permixon® with finasteride in 1,098 men with BPH

	Serum PSA (ng/ml)		Adjusted mean ratio	95% CI of adjusted mean ratio	%Δ based on adjusted mean ratio	Ratio of adjusted mean ratios	95% CI
	Baseline	26 weeks					
Permixon®	3.26 ± 3.41	3.22 ± 4.00*	1.02	0.98, 1.05	3%	1.40	1.33, 1.45 (p<0.001)
Finasteride	3.23 ± 3.34	1.99 ± 1.98	0.73	0.71, 0.75	-41%		

* not significant

Effect of age on PSA: median PSA in 32,000 healthy men

Age Group	Median PSA
40s	0.7
50s	0.9
60s	1.3
70s	1.7

(Catalona et al.)

2-Week Variation of PSA

- 84 healthy men > 50 years old
- 3 PSA measurements drawn 2 weeks apart

	Coefficient of variation (SD/Mean)
Total PSA	15%
Free PSA	17%
% Free PSA	14%

Year-to-Year PSA Fluctuations: Polyp Prevention Trial

- Retrospective analysis
- 972 male patients, median age 62
- PSA measured from annual archived sera
- Abnormal PSA outcomes measured:
 - >4 ng/ml (21% rec for bx and 44% normalized)
 - >2.5 ng/ml (37% and 40%)
 - Level above the age-specific cutoff (18% and 55%)
 - 4-10 ng/ml with free: total ratio <0.25 ng/ml (20% and 53%)
 - PSAV >0.75 ng/ml per year (15%)

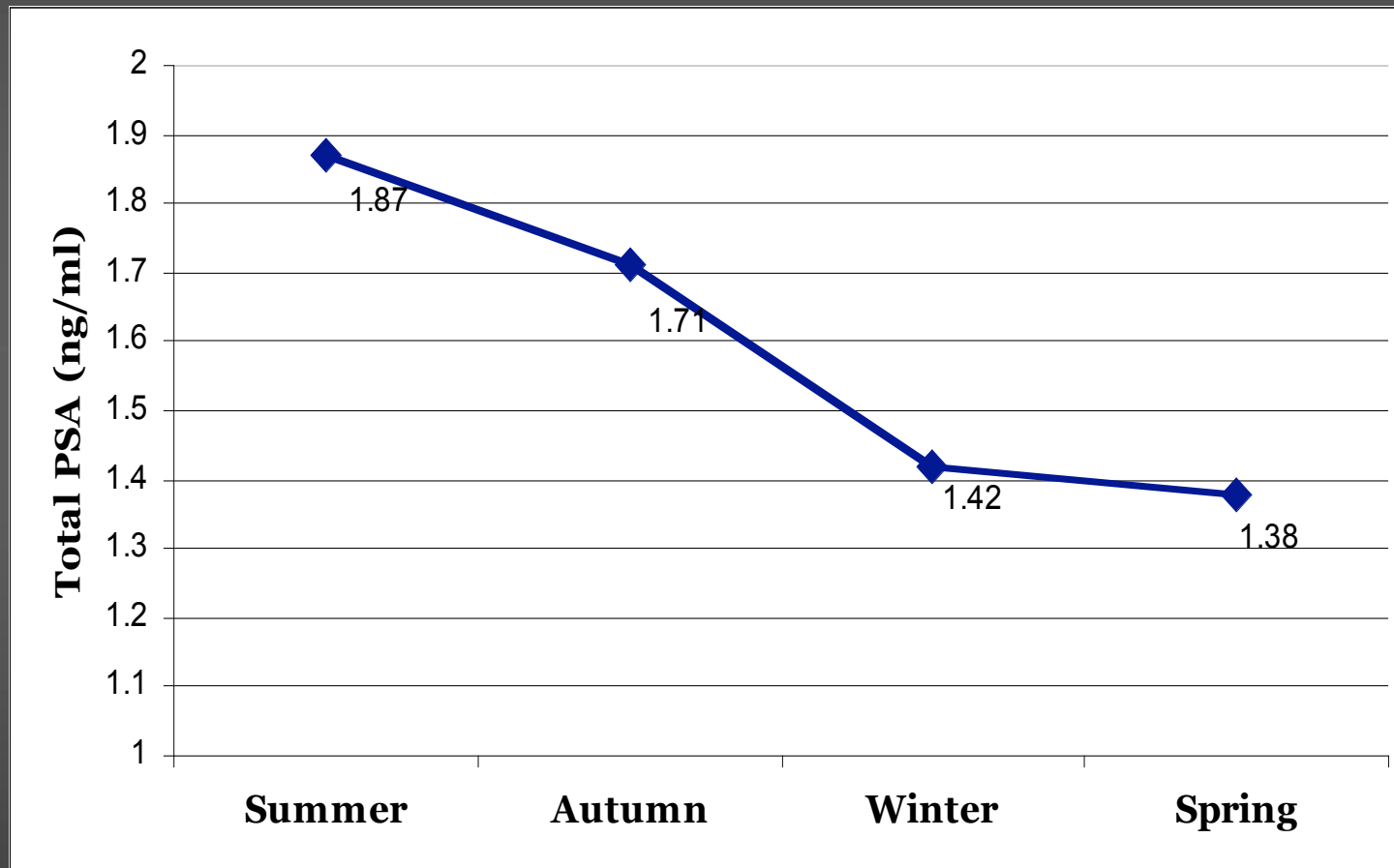
Year-to-Year PSA Fluctuations

- Results:
 - 26-37% of men with increased PSA had level return to normal on the next annual evaluation
 - 40-55% of men with increased PSA had level return to normal within 4 years
 - In 65% to 83% of those, it remained normal for years afterwards

Seasonality of PSA levels

- French arm of the European Randomized Study of Screening for Prostate Cancer (ERSPC) study
 - 8644 Participants
 - Ages 55-70
 - Observed meteorological data and correlation with total PSA and %free PSA
 - Cutoff for biopsy >3 ng/ml

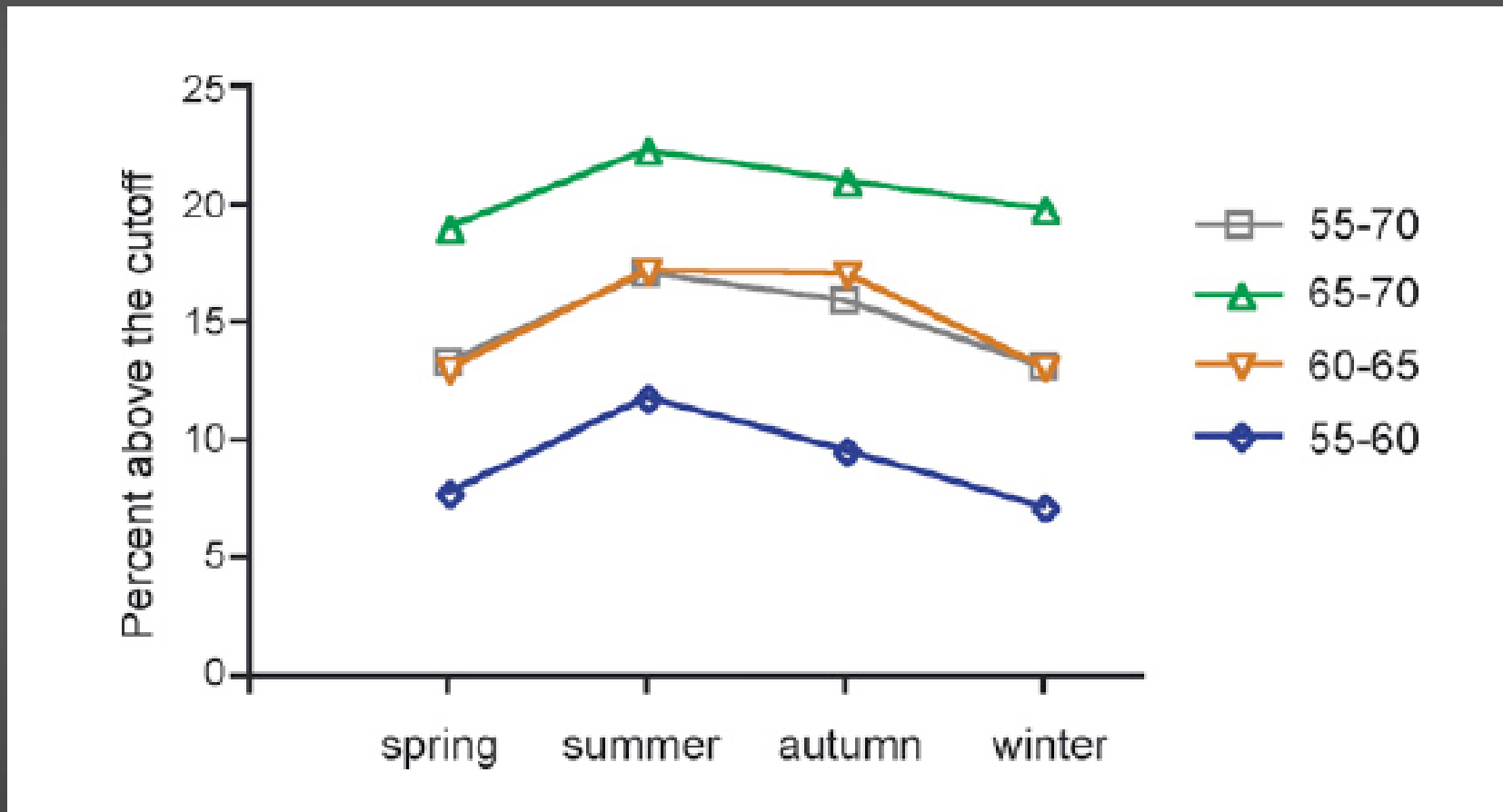
Higher PSA concentrations in summer than in other seasons (p=0.001)



Seasonality of PSA levels

- More men screened in summer had a PSA >3ng/ml (17.1%) than those screened in other seasons (14.3%), $p=0.006$
- 23% increase in the likelihood of being referred for biopsies in the summer (OR 1.23, 95% CI 1.1-1.4)
- Isolation, i.e. lack of sunshine, stratified by month also significantly correlated with total PSA levels, but not free PSA

Seasonality of PSA levels according to age



Seasonality of PSA levels

- Possible mechanisms resulting in increase
 - Androgen dependency of PSA gene expression
 - Testosterone levels peak during summer
 - Both PSA and testosterone correlate with sexual activity and ejaculation frequency
 - Vitamin D3 peaks in summer
 - Indirectly upregulates androgen receptor synthesis, nuclear localization and androgen binding
 - Melatonin lowest in summer
 - Plays a role in growth regulation, including nuclear exclusion of the androgen receptor and subsequent attenuation of the expression of androgen responsive factors
 - Dehydration
 - Plasma volume not a fixed volume

Reducing Uncertainty of PSA Levels: Antibiotic Therapy

- Theoretical advantages:
 - Treat infection
 - Cost effectiveness
 - Minimize biopsies for falsely elevated PSA
 - Decrease pt. inconvenience/morbidity
- Disadvantages:
 - Unnecessary expense
 - Potential side effects/adverse reactions
 - Increase in multi-drug resistant organisms and subsequent exposure to sepsis if biopsy becomes necessary

PSA forms increased in prostatitis

- Evaluated in 421 patients with chronic prostatitis and 112 age-matched controls
- Total PSA, free PSA, and [-2] Pro-PSA all significantly higher in patients with chronic prostatitis

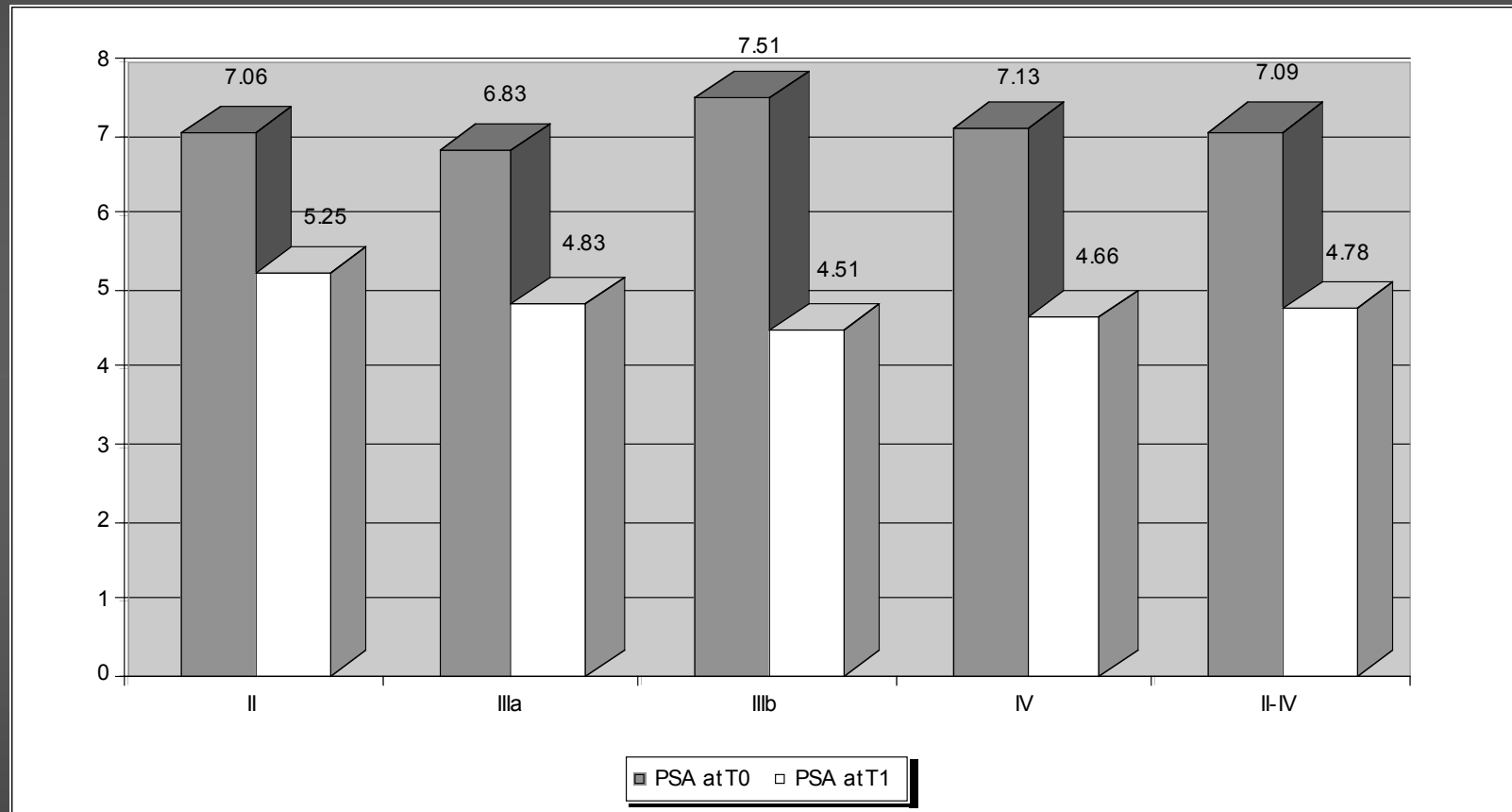
PSA Decreases with Antibiotics in Patients with Chronic Prostatitis

- PSA measured before and after 28-day course of fluoroquinolone therapy in patients with chronic bacterial prostatitis
- Median PSA decreased from 8.3 to 5.3 ng/ml
- In 42% with PSA >4 ng/ml, PSA decreased to <4ng/ml after antibiotics
- In microbiologically evaluable cases, those whose PSA normalized after therapy achieved greater success at bacterial eradication than those whose PSA remained abnormal (>90% vs. <70%)

PSA reduction after antibiotic therapy in men with chronic prostatitis

Prostatitis Category	Patients (N)	PSA reduction (%)	p-value
(CBP) II	18	25.5	0.037
(CBP/CPPS) IIIa	37	29.3	<0.0001
(CBP/CPPS) IIIb	19	40.0	0.003
Asx inflam prost) IV	37	34.6	0.0002
Total	111	32.5	<0.0001

PSA reduction after antibiotic therapy in men with chronic prostatitis



PSA normalized in 60%

Increased PSA detection rate from 12.6% to 31.1%

Magri V et al. Arch Ital Urol Androl 79: 84-92, 2007

PSA reduction after antibiotic therapy and/or anti-inflammatory agents

- In men with proven inflammation treated with antibiotic therapy, PSA returns to normal in 38-60%, similar to that of men without inflammation
- Changes after antibiotics are similar to random variations reported in healthy

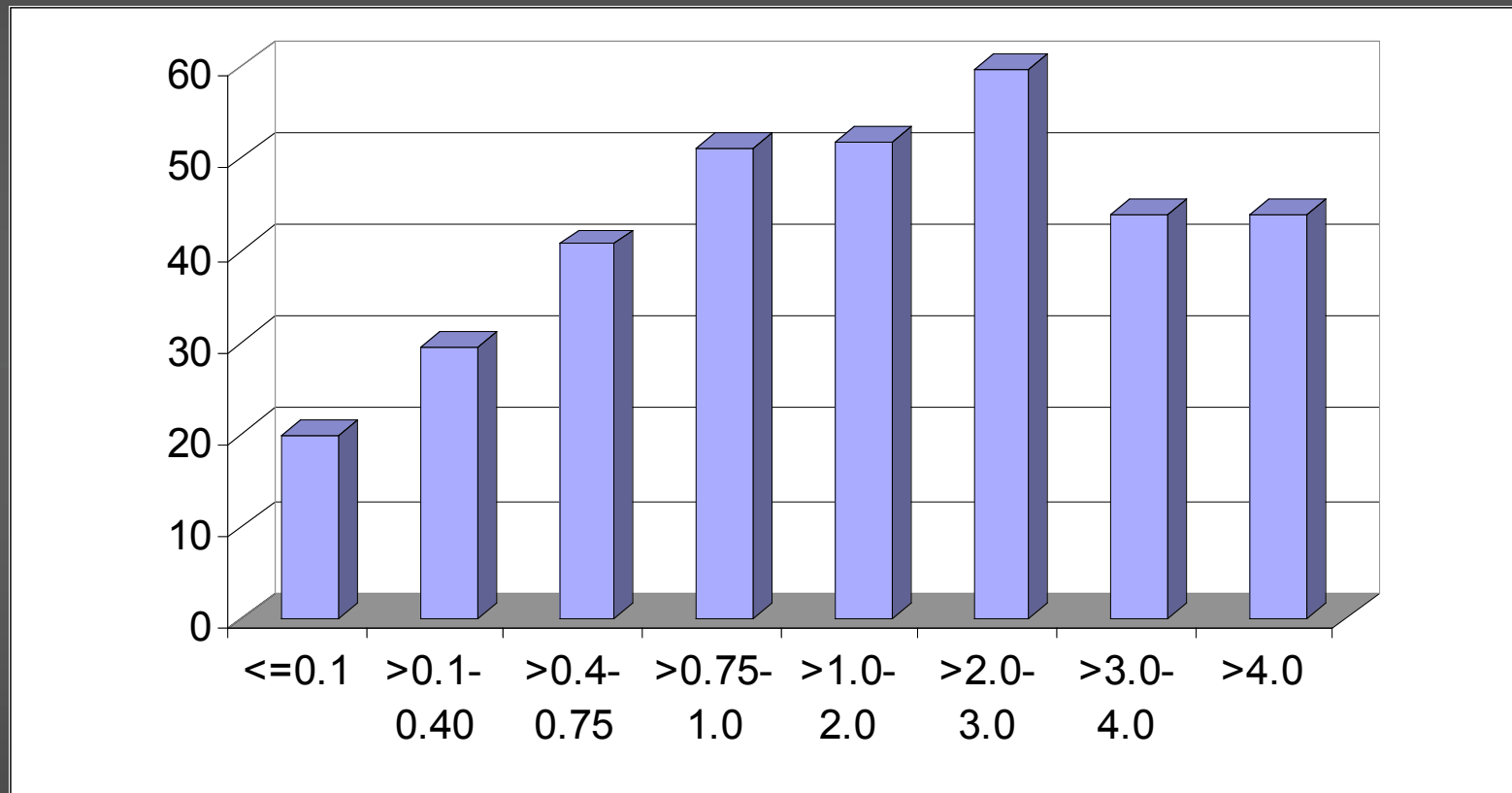
men (Kaygisiz O et al. Prost Cancer Prost Dis 2006; Erol H et al. Urol Int 2006; Tan JK et al. Singapore Med J 2002)

Potts JM. J Urol 164:1550-1553, 2000; Karazanashvili G et al. Eur Urol 39(5):538-43, 2001; Bozeman CB et al. J Urol 167(4):1723-6, 2002

Prospective Trial: Patients with elevated PSA Treated with Empiric Antibiotics (Catalona et al.)

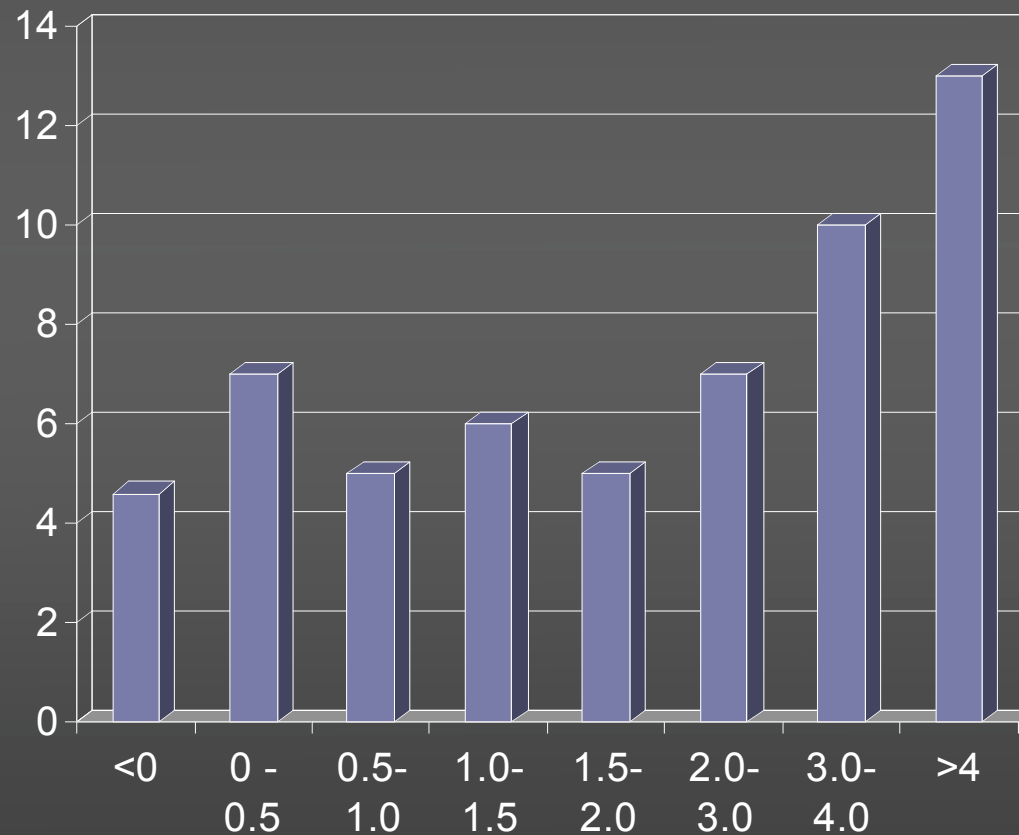
- Incorporates PSA velocity
 - PSA fluctuates more in men without CaP than in those with CaP
- Traditional PSAV cutoff for biopsy = 0.75 ng/ml/year, established in men with PSA > 4 ng/ml
- If PSA < 4 ng/ml; cutoff of 0.3-0.5 ng/ml/yr should be used
- 2007 National Comprehensive Cancer Center (NCCN) Guidelines recommend 0.35 ng/ml/year

Cancer Detection Rate by PSAV



(Catalona et al.)

Rate of prostatitis on first biopsy, stratified by PSAV

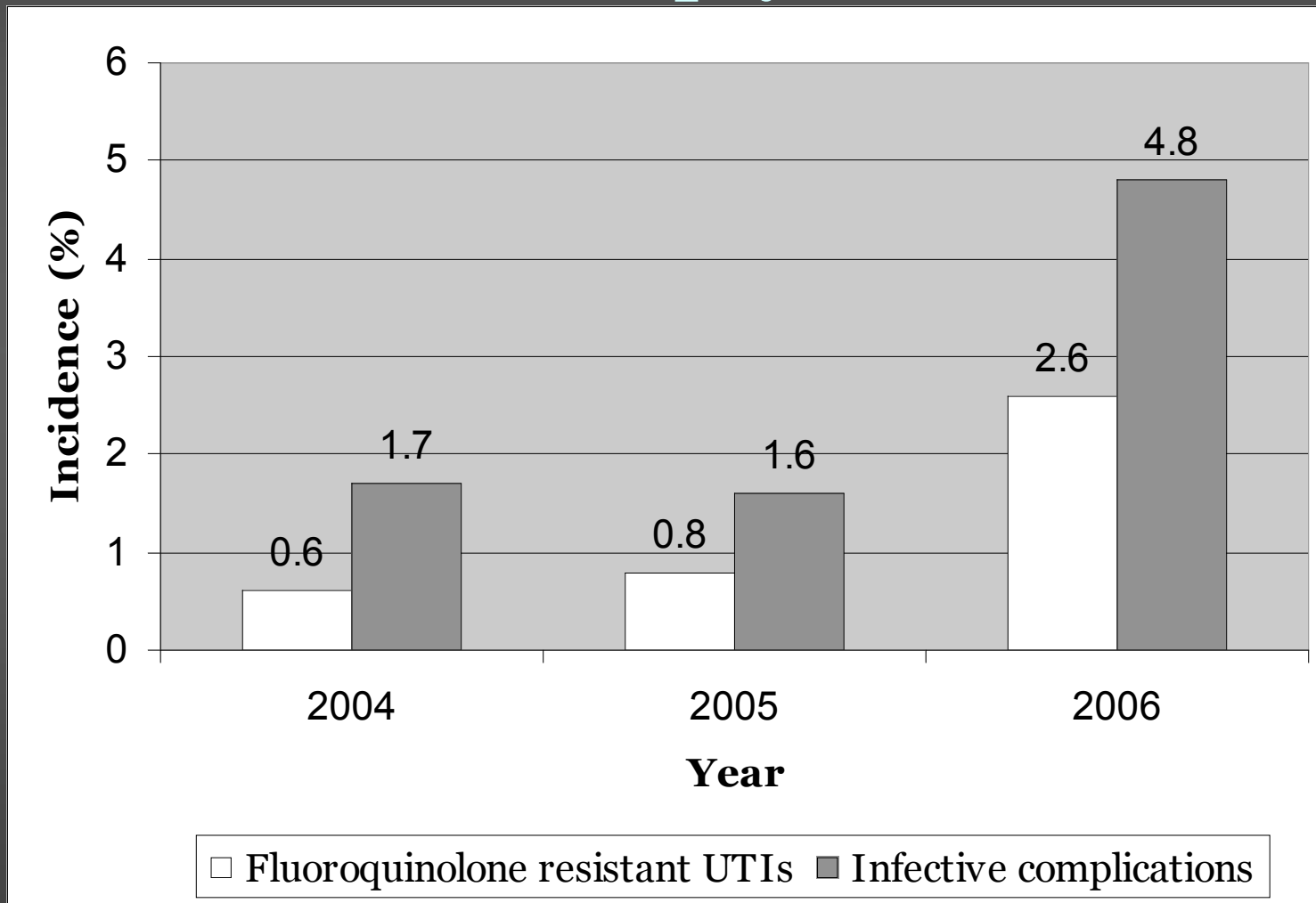


(Catalona et al.)

Caveats

- Decrease in PSA does not rule out cancer (21%)
- Lack of decrease of PSA does not rule in cancer (38%)
- Widespread use of antibiotic therapy promotes development of resistant organisms
- Exposure to antibiotic therapy before biopsy procedure may increase risk of developing complications, i.e. sepsis

Increasing drug resistance: retrospective review of 1,230 patients undergoing TRUS biopsy



Increasing drug resistance

- 91% of patients with positive cultures and fluoroquinolone resistant bacteria grew *E. Coli*
- Of these, 86% were resistant to fluoroquinolones and also resistant to ampicillin (94%), Bactrim (44%), piperacillin (72%), and gentamicin (22%)

Recommendations for use of PSA: focus on evidence-based medicine

- Rigid PSA cut-offs are ill-adapted to routine clinical practice
- Newly elevated PSA level should be confirmed before invasive tests (i.e. biopsy) are performed
- Standardize PSA assays
- Assess risk with median PSA for age group
- Use PSA density (0.1) and % free PSA (>25%) to evaluate confounding from BPH
- Use PSA velocity to identify more aggressive tumors
 - If PSA < 4 : use PSAV cutoff: 0.3 –0.5 ng/ml/yr
 - If PSA > 4: use PSAV cutoff 0.75 ng/ml/yr

Recommendations for use of Antibiotics

- An isolated increase in PSA without clear evidence of infection should not prompt antibiotic use
- Course of antibiotics is appropriate measure before recommending biopsy in patients with >20 WBC/HPF on EPS or >10 WBC/HPF on VB₃ or large fluctuations in PSA
- Wait 1 month after antibiotic therapy to let the intestinal flora “normalize” before repeating PSA and performing biopsy to avoid potential risk of sepsis