Presentation 11 – Quentin Deming & William Weiss

Successful Antibiotic Treatment Of The Gulf War Syndrome A Pilot, Randomized, Placebo Controlled, Blinded Trial

Successful Trial Of Urine Microscopy
For Control Of Antibiotic Treatment
Of Systemic Coccal Disease

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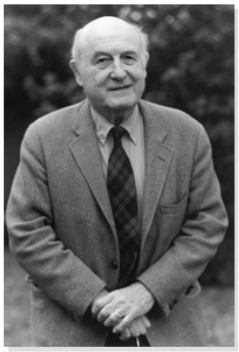
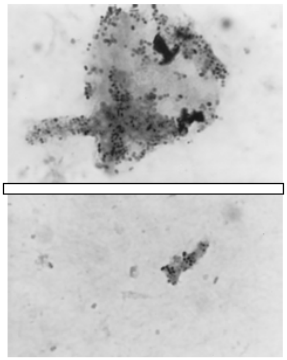
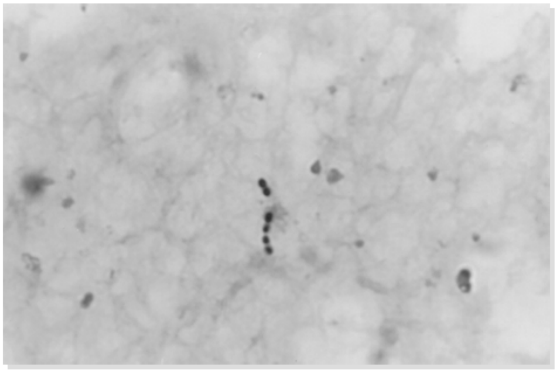


Clusters G+ cocci urine



Encapsulated cocci and shells



Flow Diagram of Protocol

Recruitment & Informed Consent (New Orleans)
!
Pre treatment Evaluation and conformity to admission criteria (SUNY Stony Brook)
!
Randomization (Kunitz & Associates-Maryland)
!
Hospitalized IV Rx, 2-3 weeks (New Orleans) *blinded*
!
oral Rx, 2 months (Home or duty) *blinded*
!
IV Rx, 5 days (New Orleans) *blinded*
!
Oral Rx, 1 mo, (Home or duty) *blinded*
!
Final Evaluation (SUNY Stony Brook) *blinded*
!
KAI breaks code & sends data to statistician

Patient Inclusion Criteria

1. Deployed to the Gulf
2. Symptoms did not pre-exist the deployment
3. Occurred by the end of 1993
4. No other explanation for the symptoms
5. Presence of Fatigue, and Impaired Cognitive Processing, plus Somatic Pain + one additional study secondary condition
6. Urine had abnormally increased excretion of GRAM positive cocci, or degenerated coccal forms

Elements of Study Design

- The sample size of 36 was calculated (using a log rank test of proportions to achieve a power (1-Type 2 error) of 80% in this trial in order to detect a change from 20% of the placebo patients demonstrating improvement to 80% of the treated patients demonstrating improvement, with a study Type-1 error of 5%, after a 4 month period of treatment.

Study Cohorts

Evaluable cohort (n=36)

Intent–to–Treat cohort (n=38)

Baseline Endpoints Variables

- **Primary Endpoints**
  1. Modified Fatigue Impact Scale (Fisk)
  2. Fatigue Assessment Inventory
  3. Neuropsych Impairment Index
- **Secondary Endpoints**
  1. Sleep Quality
  2. Headache, % patients with
  3. Median number/month
  4. Diarrhea, % ≥ 1/day
  5. Severity score ≥ 3
  6. Pain, Visual Analog Scale (McGill)
  7. Dolorimeter
  8. Quality of Life

Baseline Variables

Variables	
Demographic	4
Military Service	3
Urine Assessment	5
Exposure to Hazards	13
Endpoints	11

Baseline Characteristics

VARIABLE	PLACEBO	TREATMENT	TOTAL N
Age (years) mean	42.1	39.9	36
Race, % white	94.1	72.2	35
Sex, % male	88.9	83.3	36
Education, % college	70.6	88.9	35
Military Status, % Medical leave	6.2	11.8	33
Military Background % active duty	82.3	68.8	33
Time in Gulf Median (days)	182	197	29

Study population characteristics at baseline

Baseline Urine Variables

	Placebo	Treatment	Probability
Protein, %< 2mg/dl	52.9	33.3	0.32
Gram + cocci	29.4	27.8	1.00
Abnormal cocci+	64.7	44.4	0.31
Exploded cocci	82.4	72.2	0.69
Gram- Rods	11.8	11.1	1.0

Exposure to Hazards at Baseline

	% Exposure Placebo	% Exposure Treatment	Prob	N
Chemical warfare/nerve gas	41.7	61.5	0.43	25
Cigarette Smoke	23.1	29.4	1.00	30
Deet- Insect repellent	30.8	33.3	1.00	30
Diesel fueled tent heaters	42.9	52.9	0.72	31
Iraqi POWs	14.3	50.0	0.06	30
Oil Well Fire Smoke	64.3	82.4	0.41	31
Petroleum Contaminated H20	30.8	31.2	1.00	29
Inoculations (Pyridostigmine)	58.3	94.1	0.06	29
Ethanol Excess	0.0	0.0	1.00	30
Recreational Drug Use	0.0	0.0	1.00	30
Flea Collars	0.0	5.9	1.00	30
Pesticides, Uniform	45.4	73.3	0.23	26
Other Exposures	20.0	29.4	0.69	32

Outcome Variables at Baseline

OUTCOME VARIABLE	PLACEBO	TREATMENT	TOTAL N
Fisk, mean score (ms)	15.1	14.9	36
Fatigue Assessment Index ms)	5.9	5.9	36
Neuropsych impairment index, median score	-0.72*	-0.60	35
Sleep Quality, median score	3.5	3.7	28
Headache, % patients with	88.9	83.3	36
Median number/month	13	18.5	36
Diarrhea, % ≥ 1/day	37.5	25.0	28
Severity score ≥ 3	55.6	33.3	36
Pain, McGill, median score	6.3	6.0	36
Dolorimeter, median score	0.5	1.5	34
Quality of Life, median score	20.0	22.5	36

*one outlier excluded

Efficacy Evaluation
Primary Variables

FATIGUE

Modified Fatigue Impact Scale (Fisk)

Baseline	No statistically significant difference
Final (4 months)	p=0.0047
Final from Baseline	p=0.0074

Fatigue Assessment Inventory

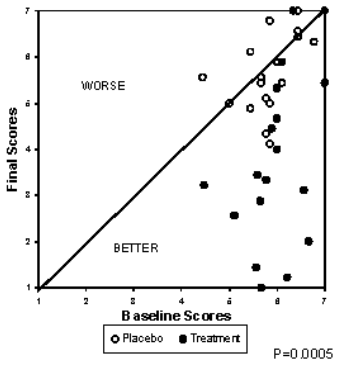
Baseline	No statistically significant difference
Final (4 months)	p=0.0005
Final from Baseline	p=0.0002

Combined Wilcoxon rank sum test p=0.0007

NEUROPSYCHOLOGICAL IMPAIRMENT INDEX

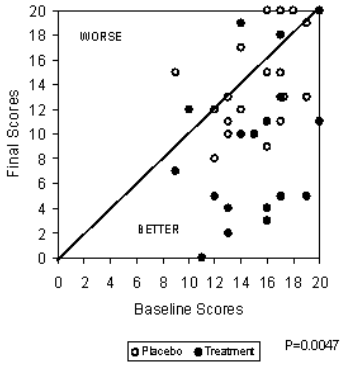
Baseline	No statistically significant difference
Final (4 months)	No statistically significant difference

Fatigue Assessment Inventory Scores

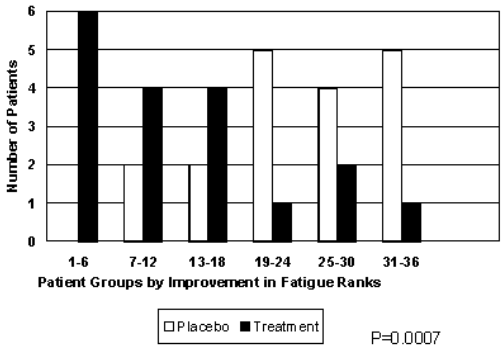


P=0.0005

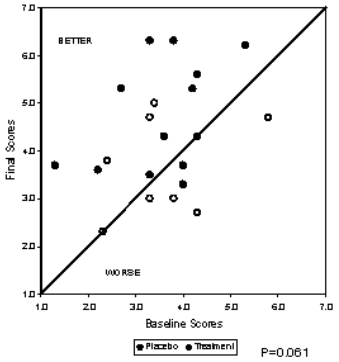
Fatigue Impact Scale - Fisk Scores



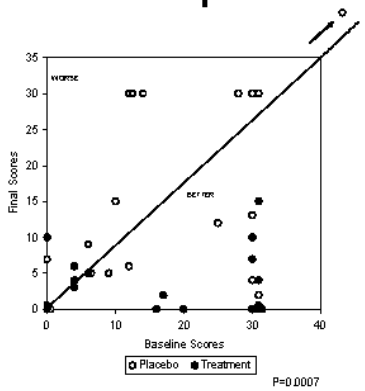
Pre-post Fatigue Scores
Combined Ranks



Sleep Rating Scores

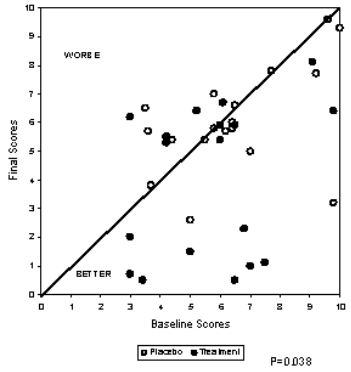


Headaches per Month

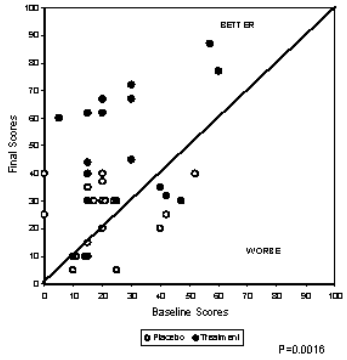


Pain: Visual Analog Scale

McGill Scores



Quality of Life Scores



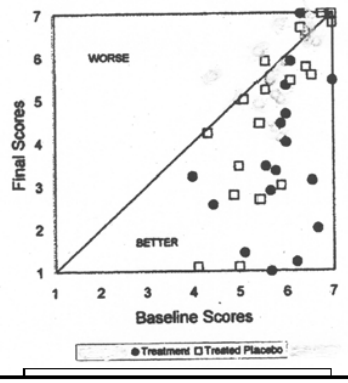
Surmise of Treatment Assignment

By Patient and Evaluator

Patient Surmise	Placebo	Patient on Treatment
Placebo	13	3
Treatment	5	15
Total	18	18

Evaluator Surmise	Placebo	Patient on Treatment
Placebo	15	3
Treatment	3	15
Total	18	18

Combined Fatigue Assessment Scores



Combined Fatigue Scores - Fisk

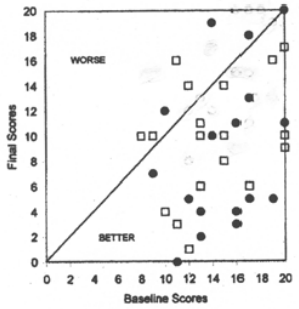
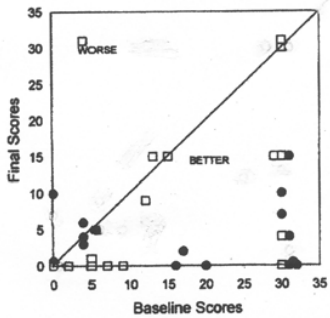


Figure 1: Modified Fatigue Impact Scale (Fisk) Scores

Combined Headaches / Month



Pain - Combined Scores

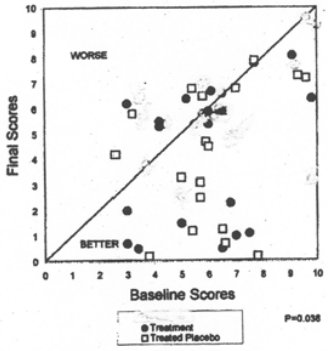


Figure 5: Pain: Visual Analog Scale (McGill) Scores

Quality of Life
Combined Scores

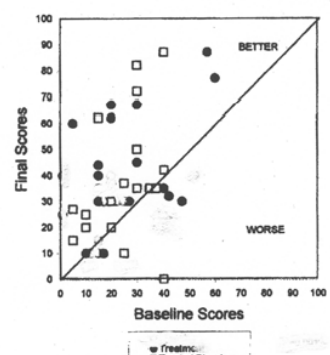
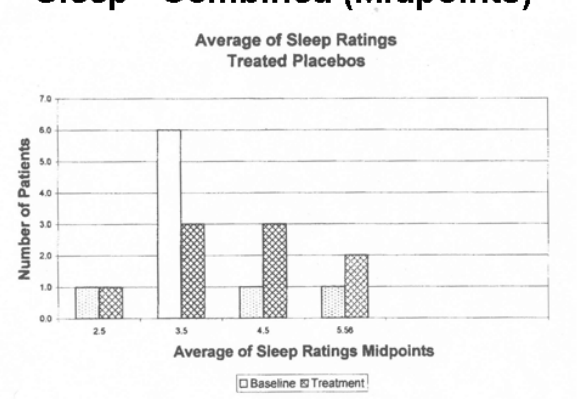


Figure 6: Quality Of Life Scores

Sleep - Combined (Midpoints)



Conclusions

- A randomized, placebo-controlled, blinded, pilot study has shown that an antibiotic regimen, controlled by monitoring excretion of Gram positive cocci, is effective in ameliorating a syndrome which affects thousands of Gulf War veterans and for which no treatment has previously been proven effective.
- The validity and effectiveness of the urine microscopy method for diagnosis and for control of treatment has been confirmed.
- The hypothesis that Gulf War Syndrome is bacterial in origin, though not proven, is supported.

Statistical Methods

1. Continuous, normally distributed variables were tested for treatment group differences by two-tailed t-tests. If the variables differed from a normal distribution, they were tested by the Wilcoxon rank sum test [12] .
2. Categorical variables, such as race and sex, were tested by a two-tailed, Fisher's exact test.
3. One of the primary outcome variables, Fatigue, is based on 2 tests; the Modified Fatigue Impact Scale (Fisk), and the Fatigue Assessment Inventory. A combined statistical analysis of these 2 tests was accomplished by a combined Wilcoxon rank sum test[13].