Global Pain & Fatigue

Differential Diagnosis and Functional Management of Common Fibromyalgia Masqueraders

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• Private Practice (Trumbull, CT)
  Whole Body Medicine

Dr. David M. Brady
Disclosures

• Chief Medical Officer: Designs for Health, Inc. (DFH)
• Chief Medical Officer: Diagnostic Solutions Labs (DSL)
• Consultant: Cell Science Systems, Inc.
Fibromyalgia

The pain of fibromyalgia is chronic, experienced in different parts of the body, not attributable to the normal mechanisms of pain, and occurs with other centrally-mediated symptoms such as: fatigue, insomnia, cognitive deficits, anxiety and depression.

**Limbic Activation**
The perception of pain in fibromyalgia differs from the normal perception of pain. This may be due in part to alterations in the limbic system which regulates responses to stressors and threats.

**HPA Activation**
Limbic activation in turn activates the hypothalamic-pituitary-adrenal axis. Fibromyalgia is associated with increased production of stress hormones, which may explain many of its symptoms such as insomnia, headache, irritable bowel, etc.

**Synaptic Excitation**
Up-regulation of the HPA axis causes increased sympathetic and parasympathetic nervous system activity. This can result in synaptic excitation in which case synapses are more sensitive to neurotransmitters that cause nerve depolarization and less sensitive to inhibitory neurotransmitters. This makes it easier to elicit a pain response from less intense stimuli.

**Central Sensitization**
In fibromyalgia, the central nervous system may be primed to perceive pain differently. Synaptic excitation may be heightened and the DANS may be down regulated. This can result in experiencing pain of greater intensity or pain from lesser stimulus. These are the classic hallmarks of fibromyalgia.

**Descending Anti-Nociceptive System (DANS)**
The DANS is an inhibitory pain pathway that constantly dampens the sensation of pain at the level of the dorsal horn of the spinal cord. In fibromyalgia, the normal pain threshold is lowered due to blunting of the DANS which may explain the heightened perception of pain.

**Substance P**
There are high levels of substance P in the spinal cord of patients with fibromyalgia. Substance P can lower the pain threshold and widen the receptive fields of pain, leading to hyperalgesia and global pain.
Central Sensitivity Syndrome

Conclusions. The findings of this study suggest that, although FM is a well-known clinical entity, differential diagnosis with SpA, CTD and inflammatory arthritis can still be a challenge for rheumatologists and general practitioners.
At the final evaluation the accuracy of the diagnosis regarding FM by either the referring physician or by the rheumatologist at the time of the initial visit was correct in 34% of patients.

Conclusion. There is a disturbing inaccuracy, mostly observed to be overdiagnosis, in the diagnosis of FM by referring physicians. This finding may help explain the current high reported rates of FM and caution physicians to consider other diagnostic possibilities when addressing diffuse musculoskeletal pain.
No Fibromyalgia Factor Test!
“Classic” FMS
- Sleep disorder
- Anxiety
- Depression
- Alterations of CNS chemistry
- Neuro-endocrine imbalances

“Pseudo - FMS”
The various disorders that are misdiagnosed as FMS
1) Organic diseases
2) Functional disorders
3) Musculoskeletal disorders

Organic
- Anemia
- Lyme disease
- Hypothyroidism
- Inflammatory arthritides
- Dysglycemia
- Occult carcinoma
- Multiple sclerosis

Functional
- Mitochondrial dysfunction
- Toxicity
- GI dysbiosis
- Nutritional deficiencies

Musculoskeletal
- Multiple TrPs
- Joint dysfunction
- Muscle imbalance
- Postural distortion
- Undiagnosed disc/facet lesions

All can be associated with fatigue and muscle tenderness

Schneider M, Brady D, Perle S.
WIDESPREAD PAIN/ FATIGUE

CLASSIC FMS

PSEUDO FMS

Organic Diseases
Many diseases cause symptoms of fatigue, exercise intolerance, soft tissue pain, etc.

- Anemias
- Hypothyroidism
- Lyme disease / Tick related illness
- Dysglycemias
- Rheumatoid arthritis (RA)
- Multiple sclerosis
- Carcinoma
- Infections
- Small Fiber Polyneuropathy
Organic Causes of Energy-Deficient States

• Initial Screen:
  – Anemia
  – Viral infection
  – Serious organic disease
  – Thyroid disorder
  – Inflammatory arthropathies

• Tools:
  – CBC and basic blood chemistry
  – Thyroid and arthritis panels
  – Predictive autoantibody panels
Anemias

“A serum ferritin level < or = to 100 mcg/L provided the best sensitivity (64.9%) and specificity (96.1%) for evaluating iron stores.... When performed within 24 hours of bone marrow examination, a serum ferritin of < or = to 100 mcg/L was 100% accurate in separating iron-deficient from iron-sufficient patients. ... None of the other serum iron indicators alone or in combination performed better than ferritin level alone.”

Anemia and H-Pylori

Eradication of H. Pylori Reverses Iron-Deficiency Anemia

"Our study," Dr. Annibale and his co-authors write, "indicates that in patients with iron-deficiency anemia and chronic H. pylori-related gastritis, cure of the infection leads to the reversal of the need for iron treatment, to normalization of hemoglobin levels after 6 months, and to long-lasting recovery from iron-deficiency anemia."

The team of researchers add that "...12 to 24 months were needed to achieve an increase in iron deposits, even if recovery from anemia was followed by a significant increase in ferritin levels (>300% over baseline), indicating a progressive build-up of body iron deposits after effective eradication [of H. pylori]."

They hypothesize that H. pylori may reduce iron absorption by causing "...a considerable decrease in the concentration of ascorbic acid in the gastric juice." In addition, the researchers comment, H. pylori "...may lead to an imbalance of body iron homeostasis..." because its "...affinity for iron binding and uptake may increase the need for iron."
Organic Acid Testing

• Pathological Assessment – Blood Chemistry & CBC

• Metabolic Assessment – Organic Acids
Methylmalonate: A Vitamin B12 Deficiency Marker

Functional Folate Marker

L-Histidine

Formiminoglutamic acid

Glutaminate Formiminotransferase

Folate

Glutamic acid

Marker of functional folic acid

“FIGLU”

Anemia Treatment

- Fix any underlying problems
- Microcytic:
  - Iron (glycinate): 30–60 mg qd until resolved on follow-up CBC
- Macrocytic:
  - Vitamin B12: 1000 mcg qd
  - Folate: 1–2 mg qd
Fatigue Evaluation

Common signs of viral infection:
- Leukocytosis ? (elevated total WBC)
- Leukocytopenia ? (depressed WBC)
- Lymphocytosis (elevated lymphocytes)
- Neutropenia (depressed neutrophils)
- Monocytosis (elevated monocytes)
- Viral titers (i.e., EBV, CMV, HSV, etc.)
- Lymphocyte sub-sets
Fatigue Evaluation (Chemistry Panel)

- Common potential signs of serious pathology:
  - High LDH
  - High alkaline phosphatase
  - Low cholesterol (<140)
  - High calcium-albumin ratio (>2.7)
  - Inverted albumin/globulin ratio (<1.0)
  - Albumin < 3.5 with lymphocyte count < 1,500
  - BUN < 8 with total protein > 8 (sign of “88”)
  - Elevated platelets

- In 50% of individuals with an unexpected platelet increase, a well-disseminated, advanced, and often inoperable malignancy will be found
Arthritic Screening (When Indicated)

Serological testing:
• RA Panel (Rheum Factor, ACCP)
• Antinuclear antibodies (ANA)
  – Anti-DNA (anti-DSNA) antibodies
  – Anti-cardiolipin
• ESR
• CRP
• Uric acid
• *Borrelia burgdorferi* (Lyme) & coinfections
  – ELISA, Western blot, PCR, cytokines, etc.
Neurological

Objective evidence that small-fiber polyneuropathy underlies some illnesses currently labeled as fibromyalgia

Anne Louise Oaklander MD PhD\textsuperscript{1,2}, Zeva Daniela Herzog BA\textsuperscript{1}, Heather Downs BS\textsuperscript{1}, and Max M. Klein PhD\textsuperscript{1}

\textsuperscript{1}Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, 02114
\textsuperscript{2}Department of Pathology (Neuropathology), Massachusetts General Hospital, Boston, Massachusetts, 02114

In conclusion, this study provides objective evidence that almost half of a small sample of patients labeled with fibromyalgia syndrome have objective evidence of a neurologic cause of their chronic widespread pain and other fibromyalgia symptoms, namely small-fiber polyneuropathy, a distinct peripheral-nerve disease.

Central Dysregulation of Thyroid

<table>
<thead>
<tr>
<th>Condition</th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td>T4 ↓ TSH ↑</td>
<td>T4 ↓ TSH ↓</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>T4 ↑ TSH ↓</td>
<td>T4 ↑ TSH ↑</td>
</tr>
</tbody>
</table>
Thyroid Hormone Cascade “Central Regulation”

- **TRH**
  - (Hypothalamus)
  - **TSH**
    - (Ant. Pituitary)
     - **T3 and T4**
      - (Thyroid)

**Negative Feedback**

(Probable)
Hypothalamus → TRH → Pituitary

Liver or Kidney

5-deiodinase

rT3
Inactive (45%)

T3
Active (35%)

5'-deiodinase (Se)

Thyroid Gland

TSH

5% T3

Cell Nucleus

~ 95%
Thyroid Screening

- Total and free T4
- Total, free, and reverse T3
- TSH
- Thyroid antibodies
Basal Body Temperature

- Axillary range (97.8–98.2°F)
- Oral range (98.2–98.6°F)
- Perform on first five days of menstrual period (preferably)
- Perform in morning before arising
- Measure for at least 10 minutes
Adrenal Stress Profile

Cortisol x 4
DHEA
sIgA
Antigliadin IgA
Neurotransmitter Metabolism

High levels:
1. Heightened sympathetic reactions in response to stress
2. Neuroblastic tumor (extreme elevations in VMA)
3. Indication for adrenal support

Neurotransmitter Metabolism Markers
(Tyrosine, Tryptophan, B6, antioxidants)

- 22 Vanilmandelate
- 23 Homovanillate
- 24 5-Hydroxyindoleacetaete
- 25 Kynurenate
- 26 Quinolinate

Methylation Cofactor Markers
(B12, Folate)

- 17 α-Keto-α-Methylvalerate
- 18 Xanthurenone
- 19 6-Hydroxyisovalerate

Cell Regulation Markers
Neurotransmitter Metabolism Markers
(Tyrosine, Tryptophan, B6, antioxidants)

- 22 Vanilmandelate
- 23 Homovanillate

Neurotransmitter Biosynthesis

- Phenylalanine → Tyrosine
- Tyrosine → Dopamine
- Dopamine → Norepinephrine
- Norepinephrine → Epinephrine

Compound in Urine

- Vanilmandelate
- Homovanillate
### Supplement Facts

**Serving Size:** 3 capsules  
**Servings Per Container:** 30

<table>
<thead>
<tr>
<th>Amount Per Serving</th>
<th>% Daily Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin C (as Ascorbic Acid)</td>
<td>100 mg</td>
</tr>
<tr>
<td>Thiamine (Vitamin B-1) (as Thiamine HCL)</td>
<td>50 mg</td>
</tr>
<tr>
<td>Riboflavin (Vitamin B-2) (as Riboflavin-5-Phosphate)</td>
<td>10 mg</td>
</tr>
<tr>
<td>Vitamin B-6 (as Pyridoxal-5-Phosphate)</td>
<td>5 mg</td>
</tr>
<tr>
<td>Vitamin B-12 (as Methylcobalamin)</td>
<td>2 mg</td>
</tr>
<tr>
<td>Pantothenic Acid (Vitamin B-5)</td>
<td>50 mg</td>
</tr>
<tr>
<td>Magnesium (as di-Magnesium Malate)</td>
<td>75 mg</td>
</tr>
<tr>
<td>Taurine</td>
<td>300 mg</td>
</tr>
<tr>
<td>L-Theanine</td>
<td>200 mg</td>
</tr>
</tbody>
</table>

**Amount Per Serving**  
**% Daily Value**

<table>
<thead>
<tr>
<th>Amount Per Serving</th>
<th>% Daily Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lemon Balm (Melissa officinalis) (leaves)</td>
<td>100 mg</td>
</tr>
<tr>
<td>Passion Flower (Passiflora incarnate) (flower)</td>
<td>100 mg</td>
</tr>
<tr>
<td>Valerian (Valeriana officinalis) (root)</td>
<td>100 mg</td>
</tr>
<tr>
<td>Ashwaganda (Withania somnifera) (root)</td>
<td>100 mg</td>
</tr>
<tr>
<td>Phosphatidylserine (from soy lecithin)</td>
<td>50 mg</td>
</tr>
</tbody>
</table>

* Daily Value not established.
# Supplement Facts

**Serving Size** 2 capsules  
**Servings Per Container** 30

<table>
<thead>
<tr>
<th>Amount Per Serving</th>
<th>% Daily Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B-6</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>(as Pyridoxal-5-Phosphate)</td>
<td></td>
</tr>
<tr>
<td>Vitamin B-12</td>
<td>1000 mcg</td>
</tr>
<tr>
<td>(as Methylcobalamin)</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>75 mg</td>
</tr>
<tr>
<td>(TRAACS® Magnesium Glycinate Chelate Buffered)</td>
<td></td>
</tr>
<tr>
<td>Inositol</td>
<td>400 mg</td>
</tr>
<tr>
<td>Taurine</td>
<td>300 mg</td>
</tr>
<tr>
<td>German Chamomile</td>
<td>200 mg</td>
</tr>
<tr>
<td><em>(Matricaria recutita)(flower)</em></td>
<td></td>
</tr>
<tr>
<td>[standardized to contain 1.2% apigenin]</td>
<td></td>
</tr>
<tr>
<td><em>gamma</em>-Aminobutyric acid</td>
<td>100 mg</td>
</tr>
<tr>
<td><em>(as PharmaGABA™)</em></td>
<td></td>
</tr>
<tr>
<td>L-Theanine</td>
<td>100 mg</td>
</tr>
<tr>
<td>5-HTP <em>(5-Hydroxytryptophan)</em></td>
<td>50 mg</td>
</tr>
<tr>
<td>Phosphatidylserine <em>(from soy lecithin)</em></td>
<td>50 mg</td>
</tr>
</tbody>
</table>

*Daily Value not established.*
WIDESPREAD PAIN/ FATIGUE

CLASSIC FMS

PSEUDO FMS

Functional Disorders
Functional Disorders

The various non-pathological disorders that represent *malfuction* of viscera:

- Toxicity
- Nutritional deficiencies
- Liver overload
- Mitochondrial dysfunction
- GI dysbiosis
- Reactive dysglycemias
- Malabsorption syndromes
- Subclinical endocrine disorders
Mitochondrial Eencephalomyopathy with Lactic Acidosis and Strokelike Episodes (MELAS): A Mitochondrial Disorder Presents as Fibromyalgia

Rowena A. DeSouza, MD, Raul J. Cardenas, MD, Tekisha L. Lindler, MD, Francisco A. De la Fuente, MD, Francisco J. Mayorquin, MD, and David S. Trochtenberg, MD, FCCP

Abstract: This case report describes a patient who presented with symptoms and signs of longstanding fibromyalgia. Routine laboratory tests revealed an elevated anion gap. Evaluation of the elevated anion gap demonstrated elevated lactate and pyruvate levels and a lactate-to-pyruvate ratio greater than 20:1. A muscle biopsy was performed, exhibiting red ragged fibers, pathognomonic for a mitochondrial disorder. The patient was diagnosed with mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes (MELAS). This is the first report describing fibromyalgia as the initial presentation of MELAS. This article outlines the diagnostic process that can assist the physician in distinguishing mitochondrial disorders from other musculoskeletal diseases, particularly fibromyalgia.

Key Words: fibromyalgia, lactic acidosis, MELAS, mitochondrial, red ragged fibers

The presenting complaint of diffuse muscular weakness and pain can be a diagnostic dilemma even for the experienced physician. One of the more common causes of these symptoms is fibromyalgia, a common malady frequently managed by the primary care physician. Fibromyalgia is defined as “widespread pain not explained by an inflammatory or degenerative musculoskeletal disorder.” The diagnosis is made on the basis of the clinical judgment of the examining physician, as there are no definitive laboratory or imaging studies. The hallmark of fibromyalgia is excessive tenderness in at least 11 of 18 points defined by the American College of Rheumatology. The estimated prevalence of fibromyalgia in the general community is 2%, occurring more commonly in women (3–4%) than in men (0.5%). The clinical presentation of mitochondrial disease has many similarities with fibromyalgia, making it possible to confuse them with one another. Mitochondrial disease, unlike fibromyalgia, is caused by abnormal oxidative metabolism of glucose within skeletal muscle, resulting in anaerobic conversion of pyruvate into lactate. The metabolic defect is the result of mutations in mitochondrial DNA. The widespread production of lactate under aerobic conditions can produce objective muscular weakness that differs from the subjective symptoms associated with fibromyalgia. Ultimately, the diagnosis of mitochondrial disease requires a thorough investigation and recognition of symptoms and signs that distinguish it from other musculoskeletal disorders, particularly fibromyalgia. The following is a case of mitochondrial disease that was initially confused with fibromyalgia.

Key Points
- Mitochondrial disease may mimic fibromyalgia.
- Unexplained elevation of the anion gap suggests mitochondrial disease.
- An elevated lactic acid level at rest and an elevated lactate-to-pyruvate ratio confirm the diagnosis of mitochondrial disease.
- Muscle biopsy displaying red ragged fibers is diagnostic of mitochondrial disease.
Elevated?

Keto acids sharing the same cofactor requirements

B₁, B₂, B₃, B₅, Lipoic Acid
B Vitamin Markers Summary

- Pyruvate: B1 and B5
- Alpha-ketoglutarate
- Alpha-keto-isovalerate
- Alpha-keto-isocaproate
- alpha-keto-beta-methylvalerate
- Xanthurenate: B6
- Beta-hydroxyisovalerate: Biotin
- Methylmalonate (MMA): B12
- Formiminoglutamate: Folic acid

B1, B2, B3, B5, lipoic acid
This report is not intended for the diagnosis of neonatal inborn errors of metabolism.

Ranges are for ages 13 and over.

**Carbohydrate Metabolism**

(8, 13, 21, 31, Lipoic acid, CoQ10)

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>1st 20%</th>
<th>2nd 40%</th>
<th>3rd 60%</th>
<th>4th 80%</th>
<th>95% Reference Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 Pyruvate</td>
<td>8.1 H</td>
<td></td>
<td></td>
<td></td>
<td>&lt;= 9.7</td>
</tr>
<tr>
<td>5 Lactate</td>
<td>44.0 H</td>
<td></td>
<td></td>
<td></td>
<td>0.8 - 54.0</td>
</tr>
<tr>
<td>6 β-Hydroxybutyrate</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
<td>&lt;= 14.5</td>
</tr>
</tbody>
</table>

**Energy Production (Citric Acid Cycle)**

(B comp, Q10, Amino acids, Mg)

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>1st 20%</th>
<th>2nd 40%</th>
<th>3rd 60%</th>
<th>4th 80%</th>
<th>95% Reference Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 Citrate</td>
<td>166</td>
<td></td>
<td></td>
<td></td>
<td>71 - 1,967</td>
</tr>
<tr>
<td>8 Cis-Aconitate</td>
<td>21 L</td>
<td></td>
<td></td>
<td></td>
<td>43 - 224</td>
</tr>
<tr>
<td>9 Isocitrate</td>
<td>91 H</td>
<td></td>
<td></td>
<td></td>
<td>57 - 157</td>
</tr>
<tr>
<td>10 a-Ketoglutarate</td>
<td>8.7</td>
<td></td>
<td></td>
<td></td>
<td>3.1 - 127.0</td>
</tr>
<tr>
<td>11 Succinate</td>
<td>66.5 H</td>
<td></td>
<td></td>
<td></td>
<td>0.7 - 99.0</td>
</tr>
<tr>
<td>12 Fumarate</td>
<td>0.31</td>
<td></td>
<td></td>
<td></td>
<td>&lt;= 1.96</td>
</tr>
<tr>
<td>13 Malate</td>
<td>2.0</td>
<td></td>
<td></td>
<td></td>
<td>&lt;= 6.6</td>
</tr>
<tr>
<td>14 Hydroxymethylglutarate</td>
<td>20.0 H</td>
<td></td>
<td></td>
<td></td>
<td>&lt;= 27.2</td>
</tr>
</tbody>
</table>
Organic Acids from Carnitine Deficiency

Fatty acids

\[ \omega-Oxidation \]

\[ \text{Adipate} \]

\[ \text{Suberate} \]

\[ \text{Ethylmalonate} \]

\[ \beta-Oxidation \]

\[ \text{Mitochondrion} \]

\[ \text{CO}_2 + \text{H}_2\text{O} + \text{ATP} \]
# L-Carnitine Markers

<table>
<thead>
<tr>
<th>Nutrient Markers</th>
<th>Results ug/mg creatinine</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fatty Acid Metabolism</strong> (Carnitine &amp; B2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Adipate</td>
<td>3.8 H</td>
<td>&lt;= 9.0</td>
</tr>
<tr>
<td>2 Suberate</td>
<td>6.5 H</td>
<td>&lt;= 13.9</td>
</tr>
<tr>
<td>3 Ethylmalonate</td>
<td>16.8 H</td>
<td>&lt;= 17.5</td>
</tr>
</tbody>
</table>
L-Carnitine and Fatigue

L-carnitine has shown encouraging results. Among complementary therapies L-carnitine has the most potential.


PMID: 18685418 [PubMed - in process]
Energy Production
This report is not intended for the diagnosis of neonatal inborn errors of metabolism.

### Energy Production (Citric Acid Cycle)

<table>
<thead>
<tr>
<th>Energy Production (Citric Acid Cycle)</th>
<th>Percentile Ranking by Quintile</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 Citrate</td>
<td>1989 H</td>
</tr>
<tr>
<td>8 Cis-Aconitate</td>
<td>139 H</td>
</tr>
<tr>
<td>9 Isocitrate</td>
<td>151 H</td>
</tr>
<tr>
<td>10 a-Ketoglutarate</td>
<td>122.3 H</td>
</tr>
<tr>
<td>11 Succinate</td>
<td>68.5 H</td>
</tr>
<tr>
<td>12 Fumarate</td>
<td>1.30 H</td>
</tr>
<tr>
<td>13 Malate</td>
<td>3.4 H</td>
</tr>
<tr>
<td>14 Hydroxymethylglutarate</td>
<td>20.0 H</td>
</tr>
</tbody>
</table>

**Severe CoQ10 Deficiency**

**All Elevated?**
### Sample Mitochondrial Support Formula #1

#### Supplement Facts

**Serving Size:** 4 capsules  
**Servings Per Container:** 30

<table>
<thead>
<tr>
<th>Amount Per Serving</th>
<th>% Daily Value</th>
<th>Amount Per Serving</th>
<th>% Daily Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiamin (Vitamin B-1) (as Thiamin HCL)</td>
<td>50 mg</td>
<td>3333%</td>
<td>Fumaric Acid (from L-Carnitine Fumarate)</td>
</tr>
<tr>
<td>Riboflavin (Vitamin B-2) (as Riboflavin-5-Phosphate)</td>
<td>10 mg</td>
<td>588%</td>
<td>D-Ribose</td>
</tr>
<tr>
<td>Vitamin B-3 (as Niacinamide)</td>
<td>5 mg</td>
<td>25%</td>
<td>Malic Acid</td>
</tr>
<tr>
<td>Vitamin B-6 (as Pyridoxal-5-Phosphate)</td>
<td>5 mg</td>
<td>250%</td>
<td>Succinic Acid</td>
</tr>
<tr>
<td>Vitamin B-12 (as Methylcobalamin)</td>
<td>2000 mcg</td>
<td>33333%</td>
<td>Natural Coenzyme Q10 (Ubiquinone)</td>
</tr>
<tr>
<td>Magnesium (as Creatine MagnaPower® Magnesium Creatine Chelate)</td>
<td>100 mg</td>
<td>25%</td>
<td>Alpha Lipoic Acid</td>
</tr>
<tr>
<td>Manganese (TRAACS® Manganese Glycinate Chelate)</td>
<td>500 mcg</td>
<td>25%</td>
<td>Trans Resveratrol from 200 mg (Polygonum cuspidatum) (root)</td>
</tr>
<tr>
<td>Curcumin C3 Complex® (Curcuma longa) (root &amp; rhizomes) (containing three curcuminoids: curcumin, bisdemethoxy curcumin, demethoxy curcumin) [standardized to contain 95% curcuminoids]</td>
<td>100 mg</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Creatine (as Creatine MagnaPower® Magnesium Creatine Chelate)</td>
<td>550 mg</td>
<td>*</td>
<td>Pantethine</td>
</tr>
<tr>
<td>L-Carnitine (as Fumarate)</td>
<td>200 mg</td>
<td>*</td>
<td></td>
</tr>
</tbody>
</table>

*Daily Value not established.*
# Sample Mitochondrial Support Formula #2

## Supplement Facts

<table>
<thead>
<tr>
<th>Amount Per Serving</th>
<th>% Daily Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhodiola (Rhodiola rosea)(root) [standardized to contain 3% rosavins and 1% salidroside]</td>
<td>300 mg *</td>
</tr>
<tr>
<td>Pyrroloquinoline quinone disodium salt (as Bio-PQQ™)</td>
<td>20 mg *</td>
</tr>
</tbody>
</table>

*Daily Value not established.*
LIVER DETOXIFICATION

TOXINS (non-polar)
- Endotoxins
- Xenobiotics

PHASE I
- Cytochrome P-450 enzymes
- Hydroxylation via redox reactions
- Critical Co-factors: NADH, NADPH, B6, Mg

INTERMEDIATE METABOLITES may be toxic

PHASE II conjugation reactions
- Glutathione Conjugation
- Amino Acid Conjugation
- Glucuronidation
- Sulfation
- Methylation
- Acetylation

EXCRETION (polar molecules)
- Kidney → Urine
- Bile → Feces
Detoxification Markers
Inorganic Sulfate from Organic Sulfur

Dietary protein (-SH, -S)

Methionine
Cysteine

Enzymes
Peptides
Matrix proteins

Glutathione

SO₄²⁻

Urinary
Sulfate

Hepatic conjugation
Antioxidant and redox balancing
Other Detox Markers

- Citrate
- cis-Aconitate
- Isocitrate
- Orotate
- 2-Methylhippurate
- Glucarate
- Alpha-Hydroxybutyrate
- Pyroglutamate

**Ammonia toxicity markers**
Need for arginine

**Detox by-product of xylene**
Need for glycine and B5

**Glucaronidation marker**
Need for glycine, glutathione, NAC

Indicates high cellular glutathione demand
Need for glutathione, NAC

Glutathione, glycine, methionine depletion
### Sample Detox Support Formula #1

#### Supplement Facts

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount Per Serving</th>
<th>% Daily Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Calories from Fat</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Total Fat</td>
<td>1 g</td>
<td>2%*</td>
</tr>
<tr>
<td>Sodium</td>
<td>150 mg</td>
<td>6%</td>
</tr>
<tr>
<td>Total Carbohydrate</td>
<td>3 g</td>
<td>1%*</td>
</tr>
<tr>
<td>Sugars</td>
<td>0 g</td>
<td></td>
</tr>
<tr>
<td>Protein (from Peatine™)</td>
<td>8 g</td>
<td>16%*</td>
</tr>
<tr>
<td>Vitamin A (as Mixed Carotenoids from Algae)</td>
<td>2500 IU</td>
<td>50%</td>
</tr>
<tr>
<td>Vitamin C (as Sodium Ascorbate)</td>
<td>250 mg</td>
<td>417%</td>
</tr>
<tr>
<td>Vitamin D (as Cholecalciferol)</td>
<td>25 IU</td>
<td>6%</td>
</tr>
<tr>
<td>Vitamin E (as d-Gamma Tocopherol)</td>
<td>100 mg</td>
<td>*</td>
</tr>
<tr>
<td>Vitamin E (as d-Alpha Tocopherol)</td>
<td>70 mg</td>
<td>*</td>
</tr>
<tr>
<td>Vitamin E (as d-Beta Tocopherol)</td>
<td>10 mg/15 IU</td>
<td>30%</td>
</tr>
<tr>
<td>Vitamin E (as Deltal Tocopherol)</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Thiamin (Vitamin B-1) (as Thiamin HCL)</td>
<td>1.5 mg</td>
<td>100%</td>
</tr>
<tr>
<td>Riboflavin (Vitamin B-2) (as Riboflavin-5-Phosphate)</td>
<td>1.5 mg</td>
<td>88%</td>
</tr>
<tr>
<td>Niacin (Vitamin B-3) (as Niacinamide)</td>
<td>4 mg</td>
<td>20%</td>
</tr>
<tr>
<td>Vitamin B-6 (as Pyridoxal-5-Phosphate)</td>
<td>2 mg</td>
<td>100%</td>
</tr>
<tr>
<td>Folate (NatureFolate™ blend)</td>
<td>50 mcg</td>
<td>13%</td>
</tr>
<tr>
<td>Vitamin B-12 (as Methylcobalamin)</td>
<td>2 mcg</td>
<td>33%</td>
</tr>
<tr>
<td>Biotin (as d-Biotin)</td>
<td>70 mcg</td>
<td>23%</td>
</tr>
<tr>
<td>Pantothenic Acid (as d-Calium Pantotenate)</td>
<td>12.5 mg</td>
<td>105%</td>
</tr>
<tr>
<td>Calcium</td>
<td>125 mg</td>
<td>13%</td>
</tr>
<tr>
<td>Iron (from Peatine™)</td>
<td>2 mcg</td>
<td>11%</td>
</tr>
<tr>
<td>Phosphorus (as Dipotassium Phosphate)</td>
<td>100 mg</td>
<td>10%</td>
</tr>
<tr>
<td>Iodine (as Potassium Iodide)</td>
<td>25 mcg</td>
<td>17%</td>
</tr>
<tr>
<td>Magnesium (TRAACS™ Magnesium Glycinate Chelate Buffered)</td>
<td>100 mg</td>
<td>25%</td>
</tr>
<tr>
<td>Zinc (TRAACS™ Zinc Glycinate Chelate)</td>
<td>3.5 mg</td>
<td>23%</td>
</tr>
<tr>
<td>Selenium (as Selenomethionine)</td>
<td>25 mcg</td>
<td>36%</td>
</tr>
<tr>
<td>Copper (TRAACS™ Copper Glycinate Chelate)</td>
<td>500 mcg</td>
<td>25%</td>
</tr>
<tr>
<td>Manganese (TRAACS™ Manganese Glycinate Chelate)</td>
<td>500 mcg</td>
<td>25%</td>
</tr>
<tr>
<td>Chromium (TRAACS™ Chromium Nicotinate Glycinate Chelate)</td>
<td>25 mcg</td>
<td>21%</td>
</tr>
<tr>
<td>Molybdenum (TRAACS™ Molybdenum Glycinate Chelate)</td>
<td>25 mcg</td>
<td>33%</td>
</tr>
<tr>
<td>Glycine</td>
<td>750 mg</td>
<td></td>
</tr>
<tr>
<td>L-Threonine</td>
<td>275 mg</td>
<td></td>
</tr>
<tr>
<td>L-Lysine</td>
<td>275 mg</td>
<td></td>
</tr>
<tr>
<td>L-Cystine</td>
<td>125 mg</td>
<td></td>
</tr>
<tr>
<td>Calcium D-Glucarate</td>
<td>125 mg</td>
<td></td>
</tr>
<tr>
<td>Quercetin</td>
<td>100 mg</td>
<td></td>
</tr>
<tr>
<td>Taurine</td>
<td>100 mg</td>
<td></td>
</tr>
<tr>
<td>Milk Thistle (Silybum marianum) (seed)</td>
<td>100 mg</td>
<td></td>
</tr>
<tr>
<td>(standardized to contain 80% silymarins)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Choline</td>
<td>50 mg</td>
<td></td>
</tr>
<tr>
<td>DL-Methionine</td>
<td>50 mg</td>
<td></td>
</tr>
<tr>
<td>Inositol</td>
<td>50 mg</td>
<td></td>
</tr>
<tr>
<td>N-Acetyl-Cysteine (NAC)</td>
<td>50 mg</td>
<td></td>
</tr>
<tr>
<td>Methylsulfonylmethane (MSM)</td>
<td>50 mg</td>
<td></td>
</tr>
<tr>
<td>Sodium Sulfate</td>
<td>50 mg</td>
<td></td>
</tr>
<tr>
<td>Green Tea</td>
<td>25 mg</td>
<td></td>
</tr>
<tr>
<td>(Camellia sinensis) (leaves)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(standardized to contain 45% ECG and 98% polyphenols)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celandine (Chelonia majus)</td>
<td>25 mg</td>
<td></td>
</tr>
<tr>
<td>Dandelion Extract (Taraxacum officinale) (root)</td>
<td>25 mg</td>
<td></td>
</tr>
<tr>
<td>Fringe Tree (Chionanthus virginicus) (bark)</td>
<td>25 mg</td>
<td></td>
</tr>
<tr>
<td>L-Glutathione</td>
<td>12.5 mg</td>
<td></td>
</tr>
<tr>
<td>Vanadium</td>
<td>25 mg</td>
<td></td>
</tr>
<tr>
<td>(TRAACS™ Vanadium Nicotinate Glycinate Chelate)</td>
<td>25 mg</td>
<td></td>
</tr>
</tbody>
</table>

*Percent Daily Values are based on a 2,000 calorie diet. Daily Value not established.

**Other Ingredients:** Tapioca dextrin, natural berry flavor, natural vanilla flavor, vegetable cellulose, stevia (leaf) extract.
## Sample Detox Support Formula #2

### Supplement Facts

**Serving Size** 6 capsules  
**Servings Per Container** 30

<table>
<thead>
<tr>
<th>Amount Per Serving</th>
<th>% Daily Value</th>
<th>Amount Per Serving</th>
<th>% Daily Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutamine</td>
<td>500 mg</td>
<td>*</td>
<td>Glutathione</td>
</tr>
<tr>
<td>Glycine</td>
<td>500 mg</td>
<td>*</td>
<td>Methionine</td>
</tr>
<tr>
<td>Methylsulfonylmethane (MSM)</td>
<td>400 mg</td>
<td>*</td>
<td>Ornithine</td>
</tr>
<tr>
<td>N-Acetyl-Cysteine</td>
<td>250 mg</td>
<td>*</td>
<td>Calcium-D-Glucarate</td>
</tr>
<tr>
<td>Taurine</td>
<td>250 mg</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Alpha Ketoglutarate</td>
<td>200 mg</td>
<td>*</td>
<td></td>
</tr>
</tbody>
</table>

*Daily Value not established.
GI Markers “Urinary Indican”
Other GI and Dysbiosis Markers

- Benzoate
- Phenylacetate
- Phenylpropionate
- p-Hydroxybenzoate
- p-Hydroxyphenylacetate
- Tricarballylate
- Dihydroxyphenylpropionate
  - (Clostridia sp.)
The Polymerase Chain Reaction is used to amplify a sample of DNA.
Bacterial colonisers of the colon comprise several hundred bacterial species that live in a complex ecosystem. Study of this complex ecosystem has been carried out, until recently, by traditional culture techniques with biochemical methods to identify organisms. The development of molecular techniques to investigate ecological microbial communities has provided the microbiologist with a vast array of new techniques to investigate human intestinal microflora. Metagenomics, the science of biological diversity, combines the use of molecular biology and genetics to identify and characterise genetic material from complex microbial environments. The combination of metagenomics and subsequent quantitation of each identified species using molecular techniques allows the relatively rapid analysis of whole bacterial populations in human health and disease.

Bacteria permanently colonise the whole length of the gastrointestinal tract with by far the highest concentration of organisms...
Gut Microbes and Systemic Pathology

Examples of epidemiologic associations between GI microbes and systemic autoimmune pathology:

- Klebsiella: Ankylosing Spondylitis
- Citrobacter, Klebsiella, Proteus: Rheumatoid Arthritis
- Yersinia: Grave’s Disease & Hashimoto’s Dz.
- S. Pyogenes: Rheumatic Fever
- Camphylobacter jejuni: Gullian Barre Syndrome
- E. coli, Proteus: Autoimmunity in general

Modified from: Mayes MD. Epidemiologic studies of environmental agents and systemic autoimmune diseases. Environ Health Perspect 1999;107(suppl. 5):743-748
**FRIEND OR FOE:** T-cells recognize foreign antigens when they are presented by the HLA molecules of the immune system. In some people, especially those who have certain HLA types, a foreign antigen may resemble antigen produced by the body. Such molecular mimicry provokes the T-cells to attack body tissues that contain the self-antigens.
Figure 2 A model linking gut to joint inflammation in spondyloarthritis. (1) Bacteria attach to and invade the intestinal epithelium and the lamina propria. HLA-B27 or CARD15 polymorphisms can result in altered recognition and handling of bacterial antigens. (2) Invading bacteria infect, or are taken up by, macrophages (M) in the lamina propria and survive intracellularly. (3) HLA-B27 can present bacterial or autologous antigens to T cells (T). Furthermore, the heavy chain easily misfolds, leading to an unfolded protein response (UPR) and stress. (4) Bacterial infection induces Th1 and Th17 responses, and IL-23R susceptibility variants, expressed on macrophages and other antigen-presenting cell types, may modulate the Th17 response. (5) More T cells and other immune mediators are recruited, releasing proinflammatory cytokines. (6) Activated T cells and macrophages carrying bacterial components migrate via blood vessels to the target joint or eventually to other sites such as skin and eye. (7) In the target joint, gut-derived macrophages and T cells recruit other immune cells and result in the activation of mesenchymal cells (MCs), which further enhance and sustain inflammation. HLA-B27, human leukocyte antigen B27; IL-23R, IL-23 receptor.
The Colonization Resistance of the Mucous Membrane of the Large Intestine in Patients with RA in a Period of Exacerbation

“The mucous membrane of healthy people is colonized by bifidobacteria, lactobacilli, *Bacteroides, Escherichia* and enterococci. The mucous membrane in RA subjects is mainly colonized by aerobic opportunistic conventionally pathogenic enterobacteria (enteropathogenic *Escherichia, Citrobacter, Enterobacter, Klebsiella*, etc.), staphylococci, enterococci and anaerobic bacteria (*Bacteroides, peptococci, peptostreptococci*, etc.). Taking into account significant changes of colonization resistance in the colon mucous membrane in remission period of RA, it is necessary to apply bacteriotherapy, using bacterial drugs containing bifidobacteria and lactobacteria.”

### Opportunistic Bacteria

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Result</th>
<th>Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campylobacter</td>
<td>Neg</td>
<td></td>
</tr>
<tr>
<td>C. difficile Toxin A</td>
<td>Neg</td>
<td></td>
</tr>
<tr>
<td>C. difficile Toxin B</td>
<td>Neg</td>
<td></td>
</tr>
<tr>
<td>E. coli O157</td>
<td>Neg</td>
<td></td>
</tr>
<tr>
<td>Enterotoxigenic E. coli LT</td>
<td>Neg</td>
<td></td>
</tr>
<tr>
<td>Enterotoxigenic E. coli ST</td>
<td>Neg</td>
<td></td>
</tr>
<tr>
<td>Shiga-like Toxin E. coli stx1</td>
<td>Neg</td>
<td></td>
</tr>
<tr>
<td>Shiga-like Toxin E. coli stx2</td>
<td>Neg</td>
<td></td>
</tr>
<tr>
<td>Salmonella</td>
<td>Neg</td>
<td></td>
</tr>
<tr>
<td>Shigella</td>
<td>Neg</td>
<td></td>
</tr>
<tr>
<td>Vibrio cholera</td>
<td>Neg</td>
<td></td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
<td>Neg</td>
<td></td>
</tr>
</tbody>
</table>

### Parasitic Pathogens

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Result</th>
<th>Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptosporidium</td>
<td>Neg</td>
<td></td>
</tr>
<tr>
<td>Entamoeba histolytica</td>
<td>Neg</td>
<td></td>
</tr>
<tr>
<td>Giardia</td>
<td>Neg</td>
<td></td>
</tr>
</tbody>
</table>

### Viral Pathogens

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Result</th>
<th>Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus 40</td>
<td>Neg</td>
<td></td>
</tr>
<tr>
<td>Adenovirus 41</td>
<td>Neg</td>
<td></td>
</tr>
<tr>
<td>Norovirus GI</td>
<td>Neg</td>
<td></td>
</tr>
<tr>
<td>Norovirus GII</td>
<td>Neg</td>
<td></td>
</tr>
<tr>
<td>Rotavirus A</td>
<td>Neg</td>
<td></td>
</tr>
</tbody>
</table>

### Helicobacter pylori

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Result</th>
<th>Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helicobacter pylori</td>
<td>&lt;dL</td>
<td>&lt;7.0 E3</td>
</tr>
<tr>
<td>Virulence Factor, cagA</td>
<td>Neg</td>
<td></td>
</tr>
<tr>
<td>Virulence Factor, vacA</td>
<td>Neg</td>
<td></td>
</tr>
</tbody>
</table>

### Normal Bacterial Flora

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Result</th>
<th>Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bifidobacter</td>
<td>6.2 E10</td>
<td>&gt;8.9 E9</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>1.3 E5</td>
<td>1.2 E4 - 3.1 E6</td>
</tr>
<tr>
<td>E. coli</td>
<td>8.1 E4</td>
<td>1.0 E4 - 7.6 E7</td>
</tr>
<tr>
<td>Lactobacillus</td>
<td>5.7 E5</td>
<td>Low</td>
</tr>
</tbody>
</table>

### Additional Tests

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Result</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA</td>
<td>523</td>
<td>510-2040 ug/mL</td>
</tr>
<tr>
<td>Anti-gliadin</td>
<td>0.2</td>
<td>0.0-6.4 ug/mL</td>
</tr>
<tr>
<td>Elastase 1</td>
<td>253</td>
<td>&gt;175 mg/g</td>
</tr>
<tr>
<td>Lactoferrin</td>
<td>3.7</td>
<td>0.0-7.2 ug/mL</td>
</tr>
<tr>
<td>Occult blood</td>
<td>Neg</td>
<td></td>
</tr>
</tbody>
</table>

### Fungi/Yeast

Candida albicans: reported as quantitative value. Other fungi/yeast are reported semi-quantitative where Low = <1000, Mod = 1,000-100,000, and High = >100,000 cfu/g stool.

The assays were developed and the performance characteristics determined by Diagnostic Solutions Laboratory.

CLIA# 11D-2097795
Medical Director - Diane Farhi, MD

DiagnosticSolutionsLab.com
<table>
<thead>
<tr>
<th>Opportunistic Bacteria</th>
<th>Potential Autoimmune Triggers</th>
<th>Result</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citrobacter spp.</td>
<td>5.0 E5</td>
<td>High</td>
<td>&lt;1.0 E4</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>8.8 E3</td>
<td>High</td>
<td>&lt;7.2 E3</td>
</tr>
<tr>
<td>Proteus spp.</td>
<td>&lt;dl</td>
<td></td>
<td>&lt;6.2 E3</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>3.9 E3</td>
<td>High</td>
<td>&lt;1.0 E3</td>
</tr>
<tr>
<td>Yersinia enterocolitica (from pg 1)</td>
<td>Negative</td>
<td></td>
<td>Neg</td>
</tr>
</tbody>
</table>

| Additional Dysbiotic/Overgrowth Bacteria   |                             |        |       |
| Morganella morganii                       | <dl                         |        | <1.0 E3 |
| Pseudomonas spp.                          | <dl                         |        | <2.5 E3 |
| Pseudomonas aeruginosa                    | <dl                         |        | <1.0 E3 |
| Staphylococcus spp.                       | 3.3 E3                      |        | <1.0 E4 |
| Streptococcus spp.                        | 9.1 E2                      |        | <1.0 E3 |
Natural Antimicrobials/Antifungals

**Antibacterial**
- Berberine herbs
- Citrus seed extract
- Oregon grape root
- Garlic
- Red Thyme Oil
- Oregano Oil
- Caprylic acid
- Uva ursi

**Antifungals**
- Berberine herbs
- Citrus seed extract
- Black walnut hull
- Garlic
- Red Thyme Oil
- Oregano Oil
- Caprylic acid
- Uva ursi

Grieve M. A modern herbal. New York: Dover 1971
Ody P. The complete medicinal herbal. London: Dorling Kindersley 1993
Sample GI Antimicrobial Support Formula #1

### Supplement Facts

**Serving Size:** 1 capsule

<table>
<thead>
<tr>
<th>Amount Per Serving</th>
<th>% Daily Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tribulus Extract (<em>Tribulus terrestris</em>) (aerial)</td>
<td>200 mg *</td>
</tr>
<tr>
<td>[standardized to contain 40% saponins]</td>
<td></td>
</tr>
<tr>
<td>Magnesium Caprylate (yielding 120 mg caprylic acid; 10 mg magnesium)</td>
<td>150 mg *</td>
</tr>
<tr>
<td>Berberine Sulfate (<em>Berberis aristata</em>) (root)</td>
<td>100 mg *</td>
</tr>
<tr>
<td>Grapefruit Extract (<em>Citrus paradisi</em>) (seed)</td>
<td>100 mg *</td>
</tr>
<tr>
<td>Barberry Extract (<em>Berberis vulgaris</em>) (bark)</td>
<td>50 mg *</td>
</tr>
<tr>
<td>[standardized to contain 6% berberine]</td>
<td></td>
</tr>
<tr>
<td>Bearberry Extract (<em>Arctostaphylos uva-ursi</em>) (leaf)</td>
<td>50 mg *</td>
</tr>
<tr>
<td>[standardized to contain 20% arbutin]</td>
<td></td>
</tr>
<tr>
<td>Black Walnut Powder (<em>Juglans nigra</em>) (hull)</td>
<td>50 mg *</td>
</tr>
<tr>
<td>Artemisinin (from Sweet Wormwood) (<em>Artemisia annua</em>) (herb)</td>
<td>15 mg *</td>
</tr>
</tbody>
</table>

*Daily Value not established.*
Supplement Facts

Serving Size 1 softgel

<table>
<thead>
<tr>
<th>Amount Per Serving</th>
<th>% Daily Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oil of Oregano</td>
<td>150 mg</td>
</tr>
<tr>
<td>(Origanum vulgare)(aerial) [a 10:1 extract equivalent to 1,500 mg of oregano]</td>
<td>*</td>
</tr>
</tbody>
</table>

*Daily Value not established.
EDDIE COLI COULDN’T UNDERSTAND WHY BUSINESS WAS BAD.
Rheumatoid arthritis is an autoimmune disease triggered by *Proteus* urinary tract infection

ALAN EBRINGER & TAHIA RASHID

School of Biomedical and Health Sciences, Kings College London, London, UK

Abstract

Rheumatoid arthritis (RA) is a chronic and disabling polyarticular disease, which affects mainly women in middle and old age. Extensive evidence based on the results of various microbial, immunological and molecular studies from different parts of the world, shows that a strong link exists between *Proteus mirabilis* microbe and RA. We propose that sub-clinical *Proteus* urinary tract infections are the main triggering factors and that the presence of molecular mimicry and cross-reactivity between these bacteria and RA-targeted tissue antigens assist in the perpetuation of the disease process through production of cytokine autoantibodies.

Patients with RA especially during the early stages of the disease could benefit from *Proteus* anti-bacterial measures involving the use of antibiotics, vegetarian diets and high intake of water and fruit juices such as cranberry juice in addition to the currently employed treatments.

Keywords: Hemeral autotoimmunity, *Proteus mirabilis*, rheumatoid arthritis, urinary tract infection

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease, which affects millions of people all around the world, with a prevalence rate ranging from 0.5 to 1% (Lawrence et al. 1998). The disease in the majority of patients takes a mild to moderate course, whilst in others it has a more disabling consequence, which might have a great effect on the socio-economic status of the patient (Cooper 2000). RA affects individuals of middle age groups and occurs three times more frequently in women than in men.

Aetio-pathogenesis

A general scientific consensus exists, which considers RA as an immune-mediated disease that could possibly be triggered by an environmental (microbial) factor in a genetically susceptible individual. Extensive evidence supports the role of cellular and humeral autoimmunity in the development of RA, and some of these are listed as follows:

1. Predominant role of B lymphocytes in the pathogenesis of RA (Weyand et al. 2005) and signs of accumulations of immunoglobulins and other inflammatory products such as complements at the site of synovial pathological lesions in RA patients (Low and Moore 2005).

2. Detection of elevated levels of auto-antibodies in the serum and/or synovial fluid of patients with RA (Rasenberg-Dahlqvist 2005).

3. Significant improvements in RA disease parameters following B cell depletion therapy, e.g. with the use of anti-CD20 antibodies (Perosa et al. 2005).

Role of HLA genes in RA

The role of genetics in development of RA has been examined mainly through family, twin and molecular analytical studies. For instance, familial distribution of RA among first-degree relatives (Deighton et al. 1992a) and twins (MacGregor et al. 2000), indicates that RA runs in some families, basically supporting the

**Rheumatoid arthritis: proposal for the use of anti-microbial therapy in early cases**

Alan Ehringer1, Taha Rashid1, and Clyde Wilson1

1Division of Life Sciences, Infection and Immunity Group, King’s College London, 2Department of Rheumatology, Middlesex Hospital, University College, London, UK

Rheumatoid arthritis (RA) is a chronic disease, affecting women more than men, especially in those possessing the “shared epitope” (EQS/RRAA) amino acid sequence present in HLA-DR14 molecules. *Proteus mirabilis* carries certain sequence showing molecular mimicry to the “shared epitope” and to type II collagen of human cartilage. Elevated levels of antibodies to *Pseudomonas* bacteria have been reported from 14 different countries involving 1372 RA patients and the microbe has been isolated from urine cultures of such patients. Our working hypothesis is that the disease develops as a result of repeated episodes of *Proteus* upper urinary tract infections. Prospective studies involving the trial of anti-*Proteus* measures in RA patients should be evaluated in the management of this disease. Antibiotics, high fluid intake, and fruit extracts, such as cranberry juice, have all been found to be effective in the treatment of urinary tract infections. Such measures could be used as possible additional adjuncts to the standard therapy with NSAIDs and DMARDs.

Key words: rheumatoid arthritis, *Proteus* urinary tract infections, diet

More than 25 years ago a significant discovery was made when the HLA-DR4/Dw4 genetic marker was found in 80% of the patients with RA, using both mixed lymphocyte culture assay (7) and serological methods. As (8) it was observed that only certain types and subtypes of HLA-DR molecules were associated with RA. The third hypervariable regions of all RA-associated HLA-DR alleles were found to share a hexameric amino acid sequence homology involving positions 69-74 and consisting of glutamic acid, glutamine, lysine or arginine, arginine, alanine, and serine (EQS/RRAA). This sequence similarity in RA, which has been given the name of “shared epitope” (SE) (9) motif, was not found in either HLA-DR molecules, like HLA-DR2 (10) or HLA-DR4 (11), which are not associated with RA.

Regardless of the difference in the distribution of HLA genes among various ethnic groups, it has been reported that more than 95% of patients possess one or another of the RA-linked HLA-DR molecules (10) which contain the SE motif. These include HLA-DR4 subtypes (DRB1*0401, *0404, *0405 and *0408), HLA-DR1 subtypes (DRB1*0101 and 0102), HLA-DR (DRB1*0401 and 0402), which is not associated with RA.

The importance of SE amino acid sequences in conferring susceptibility to RA is not only confined to humans, but also to animals such as the canine species. (13) The mere association of the SE mRNA with RA, however, is not necessarily sufficient to trigger the disease. In spite of a positive correlation between the presence of DR4 and SE homozygosity
Molecular Mimicry: Proteus and HLA-DR1/DR4

A: ESRRAL sequence of *Proteus mirabilis* haemolysin
B: EQRRAA sequence within DRB1*0101 (HLA-DR1)
C: EDERAA sequence of DRB1*0402 (HLA-DR4/Dw10)
(predicted from known crystallographic structure)

Alan Ebringer, MD
King’s College, London
Table II. Possible explanation for some commonly encountered features in RA.

<table>
<thead>
<tr>
<th>Associated RA Features</th>
<th>Suggested Explanations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female preponderance 3:1</strong></td>
<td>Increased incidence of UTIs in females</td>
</tr>
<tr>
<td>Disease onset in 30–50 years</td>
<td>Increased incidence of UTIs among middle and older age groups</td>
</tr>
<tr>
<td>Exacerbation after pregnancy</td>
<td>Increased incidence of UTIs in the puerperium</td>
</tr>
<tr>
<td><strong>Low concordance rate</strong> in identical twins and fluctuating course of the disease</td>
<td>Involvement of non-genetic environmental factors in the pathogenesis of the disease</td>
</tr>
<tr>
<td>Presence of <strong>rheumatoid factors</strong> in high proportions of RA patients</td>
<td><strong>A secondary phenomenon</strong> due to B cell stimulation and presence of antigen-antibody complexes</td>
</tr>
<tr>
<td>Presence of &quot;EORRAA&quot; amino acid motif in over 95% of patients possessing the RA-associated HLA-DR molecules</td>
<td>Cross-reactivity with &quot;ESRRAL&quot; amino acid sequences present in the <em>Proteus hemolysins</em></td>
</tr>
<tr>
<td>High proportion of <strong>small joints</strong> involvement, having hyaline cartilage which contains type XI collagen, possessing the &quot;IRRET&quot; amino acid sequence</td>
<td>Cross-reactivity with &quot;LRREI&quot; amino acid motif present in the <em>Proteus urease</em> enzyme</td>
</tr>
</tbody>
</table>

*Scand J Rheumatol 2003;32:2–11*

**REVIEW**

**Rheumatoid arthritis: proposal for the use of anti-microbial therapy in early cases**

Alan Ebringer1,2, Taha Rashid1, and Clyde Wilson1
Fig. 2. Proposed schematic representation for the identification and treatment of patients with Proteus reactive arthritis and early RA.
Sample UT Antimicrobial Support Formula

**Supplement Facts**

Serving Size 2 capsules
Servings per container 30

<table>
<thead>
<tr>
<th>Amount Per Serving</th>
<th>% Daily Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B-6 (as Pyridoxal-5-Phosphate)</td>
<td>10 mg</td>
</tr>
<tr>
<td>D-Mannose</td>
<td>500 mg</td>
</tr>
<tr>
<td>Bearberry Extract <em>(Arctostaphylos uva ursi)</em> (leaf) [standardized to contain 20% arbutin]</td>
<td>200 mg</td>
</tr>
<tr>
<td>UTIRose™ Hibiscus Extract <em>(Hibiscus sabdariffa)</em> (flower)</td>
<td>200 mg</td>
</tr>
<tr>
<td>Nettle <em>(Urtica dioica)</em> (root) [standardized to contain .8% ß-sitosterol]</td>
<td>200 mg</td>
</tr>
<tr>
<td>Aloe Vera <em>(Aloe barbadensis)</em> (leaf) (200:1)</td>
<td>125 mg</td>
</tr>
<tr>
<td>Parsley Powder <em>(Petroselinum crispum)</em> (leaf)</td>
<td>100 mg</td>
</tr>
<tr>
<td>Horsetail Extract <em>(Equisetum arvense)</em> (stem) [standardized to contain 7% silica]</td>
<td>50 mg</td>
</tr>
</tbody>
</table>

*Daily Value not established.*
“It may, therefore, be assumed that the gram-negative bacterium Yersinia enterocolitica may have an active part in triggering immunogenic thyroid diseases....”

Petru G, Stunzner D, Lind P, Eber O, Mose JR.
### Predominant Bacteria

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>CFU/gram</th>
<th>1st Quartile</th>
<th>2nd Quartile</th>
<th>3rd Quartile</th>
<th>4th Quartile</th>
<th>5th Quartile</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteroides sp.</td>
<td>1.1</td>
<td>1.6</td>
<td>1.5</td>
<td>1.6</td>
<td>6.7</td>
<td>6.2</td>
<td>=&gt; 1.3</td>
</tr>
<tr>
<td>Clostridia sp.</td>
<td>3.2</td>
<td>1.5</td>
<td>1.6</td>
<td>6.2</td>
<td>6.2</td>
<td>6.0</td>
<td>=&gt; 1.0</td>
</tr>
<tr>
<td>Prevotella sp.</td>
<td>14.5</td>
<td>1.6</td>
<td>1.6</td>
<td>6.2</td>
<td>6.2</td>
<td>6.2</td>
<td>=&gt; 1.1</td>
</tr>
<tr>
<td>Fusobacteria sp.</td>
<td>3.3</td>
<td>1.6</td>
<td>1.6</td>
<td>7.4</td>
<td>7.0</td>
<td>7.0</td>
<td>=&gt; 1.1</td>
</tr>
<tr>
<td>Streptomyces sp.</td>
<td>17.3</td>
<td>1.7</td>
<td>1.8</td>
<td>5.8</td>
<td>6.2</td>
<td>6.2</td>
<td>=&gt; 1.2</td>
</tr>
<tr>
<td>Mycoplasma sp.</td>
<td>17.7</td>
<td>1.7</td>
<td>1.8</td>
<td>5.8</td>
<td>6.2</td>
<td>6.2</td>
<td>=&gt; 1.2</td>
</tr>
</tbody>
</table>

### Opportunistic Bacteria

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>CFU/gram</th>
<th>1st Quartile</th>
<th>2nd Quartile</th>
<th>3rd Quartile</th>
<th>4th Quartile</th>
<th>5th Quartile</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yersinia enterocolitica</td>
<td>2.3E+08</td>
<td>H</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;= 1.0E+05</td>
</tr>
</tbody>
</table>

### Units and Reference Ranges

Organisms are detected by DNA analysis. One colony forming unit (CFU) is equivalent to one bacterium. Each genome detected represents one cell, or one CFU. Results are expressed in scientific notation, so an organism reported as 2.5 E7 CFU/gram is read as 25 million colony forming units per gram of feces. The cutoff for significance of Opportunistic Bacteria has been set at 1.0E+005 (100,000). These are levels above which clinically significant growth may be present. Rather than reporting semi-quantitative +1 to +4 levels, the new methodology provides full quantitative analysis.

**Predominant Bacteria** play major roles in health. They provide colonization resistance against potentially pathogenic organisms, aid in digestion and absorption, produce vitamins and SCFA’s, and stimulate the GI immune system. DNA probes allow detection of multiple species (sp.) within a genus, so the genera that are reported cover many species.

**Opportunistic Bacteria** may cause symptoms and be associated with disease. They can affect digestion and absorption, nutrient production, pH and immune state. Antibiotic sensitivity tests will be performed on all opportunistic bacteria found, although clinical history is usually considered to determine treatment since the organisms are not generally considered to be pathogens.

**Taxonomy Unavailable**

Gifx will detect DNA from all commonly reported organisms in microscopic parasitology. In addition, any DNA present from yeast/fungi or protozoa will also be detected. These are reported as positive, taxonomy unavailable.
Abstract

Viral infections are frequently cited as a major environmental factor involved in subacute thyroiditis and autoimmune thyroid diseases. This review examines the data related to the role of viruses in the development of thyroiditis.

Our research has been focused on human data. We have reviewed virological data for each type of thyroiditis at different levels of evidence; epidemiological data, serological data or research on circulating viruses, direct evidence of thyroid tissue infection. Interpretation of epidemiological and serological data must be cautious as they don’t prove that this pathogen is responsible for the disease. However, direct evidence of the presence of viruses or their components in the organ are available for retroviruses (HFV) and mumps in subacute thyroiditis, for retroviruses (HTLV-I, HFV, HIV and SV40) in Graves’s disease and for HTLV-I, enterovirus, rubella, mumps virus, HSV, EBV and parvovirus in Hashimoto’s thyroiditis. However, it remains to determine whether they are responsible for thyroid diseases or whether they are just innocent bystanders. Further studies are needed to clarify the relationship between viruses and thyroid diseases, in order to develop new strategies for prevention and/or treatment.
Silver 'boost to antibiotic success'

Adding silver to antibiotics makes them 10 to 1,000 times more effective at fighting infections, research suggests. Silver has been used as an antimicrobial for centuries, but little has been known about how it works. The new research suggests adding it to existing antibiotics could counteract the rise of drug-resistant microbes. Experiments in mice showed the metal disrupts the biological processes of bacteria, making them more permeable to antibiotics, a US team reports. Bacteria are adapting and finding ways to survive the effects of antibiotics. According to England's chief medical officer, Prof Dame Sally Davies, antibiotics are losing their effectiveness at a rate that is both alarming and irreversible. Silver acts against Gram-negative bacteria - one of the two main types of bacteria - which are particularly difficult pathogens to treat. The research was led by Jose Ruben Morones-Ramirez of the Howard Hughes Medical Institute at Boston University.

He told the journal Science Translational Medicine: "This work shows that silver can be used to enhance the action of existing antibiotics against Gram-negative bacteria, thus strengthening the antibiotic arsenal for fighting bacterial infections." Future studies will focus on testing how silver can be added to antibiotic injections or tablets for use in patients.
Autoimmune Thyroid Disease and Celiac Disease

Celiac patients have approximately 10 times the rate of autoimmune thyroid diseases, such as Hashimoto’s thyroiditis and Grave’s disease, as non-celiac individuals.

Figure 3: Changing carbohydrate intake patterns

The two pie charts compare the carbohydrate intake patterns of primitive and modern man. Note the extremely high intake of essential sugar-rich fruits, roots, nuts and legumes of the former (1).

**Intake of carbohydrates**

- **Primitive man**
  - 99% vegetables, fruits, roots, legumes, nuts
  - 1% whole cereal grains

- **Modern man**
  - 59% refined grains
  - 18% refined/artificial sugars, sweeteners
  - 23% vegetables, fruits, legumes, nuts
Food Sensitivity Testing

Pre-antigen exposure

Post-antigen exposure
This observation supports the hypothesis that non-celiac gluten sensitivity may be an underlying cause of FM syndrome.
WIDESPREAD PAIN/FATIGUE

CLASSIC FMS

PSEUDO FMS

Musculoskeletal Disorders
Musculoskeletal Disorders

The various mechanical disorders that often give a false impression of “widespread pain”:

• Myofascial referred pain
• Scleratogenous referred pain
• Discogenic pain
• Chronic neuromusculoskeletal pain that has become ill defined
# Myofascial Pain Syndrome vs. FMS

<table>
<thead>
<tr>
<th>Myofascial Pain</th>
<th>Fibromyalgia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>REGIONAL PAIN</strong></td>
<td><strong>GLOBAL PAIN</strong></td>
</tr>
<tr>
<td>Trigger Points (TrPs)</td>
<td>Tender Points (TePs)</td>
</tr>
<tr>
<td>No Fatigue</td>
<td>Fatigue, “Fibro-Fog”</td>
</tr>
<tr>
<td>Normal Sleep</td>
<td>Disturbed Sleep</td>
</tr>
<tr>
<td>Muscle Dysfunction</td>
<td>CNS Dysfunction</td>
</tr>
<tr>
<td>Regional Referred Pain Patterns</td>
<td>Central Allodynia, (i.e., Widespread Pain)</td>
</tr>
</tbody>
</table>
FMS Pain Diagram

FMS and/or Somatization Disorder

Regional Myofascial Pain Syndrome
Trigger Points vs. Tender Points

• Not synonymous terms

• TrPs have a distinct texture of feeling like knots or nodules; found within a taut band of muscle tissue

• TePs have no palpable tissue texture abnormalities; they are merely areas that feel tender

• Therefore, any literature that mixes the terms TeP and TrP, or myofascial pain syndrome and FMS, is flawed and faulty
TrPs are affected via neural reflexes
Elongated sarcomeres

TrP nodule = focus of contracted sarcomeres

Normal sarcomeres
“Pseudo-Widespread Pain”
from Myofascial Referred Pain Patterns
Fibromyalgia patients who have experienced deep muscle compression therapy know that direct sustained pressure eases soft tissue pain and opens the door to improved muscle function and increased range of motion. With its free 35 page User Guide, the Original Backnobber® II lets you locate your pain sites and apply tension-releasing pressure, enabling you to manage your symptoms.
Muscle Dysfunction/ Myofascial Pain

- Ischemic compression
- PIR, MET, ART procedures
- Myofascial release techniques
- Elimination of TrPs and muscle tightness, thereby restoring normal proprioceptive input to CNS
Sample Muscle Relaxant Support Formula

<table>
<thead>
<tr>
<th>Supplement Facts</th>
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<tbody>
<tr>
<td>Serving Size 3 capsules</td>
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<td>Servings Per Container 40</td>
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<table>
<thead>
<tr>
<th>Amount Per Serving</th>
<th>% Daily Value</th>
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<tr>
<td>Calcium</td>
<td>75 mg 8%</td>
</tr>
<tr>
<td>(as DimaCal® Di-Calcium Malate)</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>150 mg 38%</td>
</tr>
<tr>
<td>(as Di-Magnesium Malate)</td>
<td></td>
</tr>
<tr>
<td>Valerian</td>
<td>100 mg *</td>
</tr>
<tr>
<td><em>(Valeriana officinalis)</em>(root)</td>
<td></td>
</tr>
<tr>
<td>[standardized to contain 0.8% valerenic acid]</td>
<td></td>
</tr>
<tr>
<td>Passion Flower</td>
<td>100 mg *</td>
</tr>
<tr>
<td><em>(Passiflora incarnata)</em>(flower)</td>
<td></td>
</tr>
<tr>
<td>[standardized to contain 3.5% flavonoids]</td>
<td></td>
</tr>
<tr>
<td>Lemon Balm</td>
<td>75 mg *</td>
</tr>
<tr>
<td><em>(Melissa officinalis)</em>(leaves)</td>
<td></td>
</tr>
<tr>
<td>[standardized to contain 3% rosmarinic acid]</td>
<td></td>
</tr>
<tr>
<td>Skullcap</td>
<td>25 mg *</td>
</tr>
<tr>
<td><em>(Scutellaria lateriflora)</em>(root)</td>
<td></td>
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</tbody>
</table>

*Daily Value not established.*
Eliminate the Cause

- Joint dysfunction/subluxation
- Disc lesions
- Muscle dysfunction
- CNS dysfunction/poor motor control
“Pseudo-Widespread Pain” from Scleratogenous Referred Pain Patterns
Joint Dysfunction

- Mobilization
- Manipulation
- Chiropractic/osteopathic and manual techniques that restore normal joint alignment and function
- Restoration of normal proprioceptive input and removal of noxious somato-somato reflexes
Disc Lesions

- Traction methods
- Mobilization/manipulation
- McKenzie exercise method
- Epidural steroid injections
- Surgery
Arachidonic Acid Metabolism

No Treatment

Traditional NSAIDs

COX-2 Inhibitors

Normal

Ulceration

Edema

Dyspepsia

Hypertension

Renal Dysfunction

CV Dysfunction

AA

COX-1

COX-2

5-LOX

JOURNAL OF MEDICINAL FOOD
J Med Food 10 (3) 2007, 442–451
### Supplement Facts

**Serving Size:** 2 capsules  
**Servings Per Container:** 30

<table>
<thead>
<tr>
<th>Amount Per Serving</th>
<th>% Daily Value</th>
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<tbody>
<tr>
<td>InflammENZ™ Proprietary Blend</td>
<td>222 mg</td>
</tr>
<tr>
<td>Protease, Serratiopeptidase</td>
<td></td>
</tr>
<tr>
<td>Protease SP, Trypsin, Chymotrypsin</td>
<td></td>
</tr>
<tr>
<td>Curcumin C3 Complex®</td>
<td>200 mg</td>
</tr>
<tr>
<td><em>(Curcuma longa)(rhizomes)</em></td>
<td></td>
</tr>
<tr>
<td><em>(containing three curcuminoids: curcumin, bisdemethoxy curcumin, demethoxy curcumin)</em></td>
<td></td>
</tr>
<tr>
<td><em>(standardized to contain 95% curcuminoids)</em></td>
<td></td>
</tr>
<tr>
<td>Boswellia (as Boswellin® Extract)</td>
<td>200 mg</td>
</tr>
<tr>
<td><em>(Boswellia serrata)(resin)</em></td>
<td></td>
</tr>
<tr>
<td><em>(standardized to contain 60% boswellic acids)</em></td>
<td></td>
</tr>
<tr>
<td><strong>Amount Per Serving</strong></td>
<td><strong>% Daily Value</strong></td>
</tr>
<tr>
<td>Ginger Extract <em>(Zingiber officinale)(root)</em></td>
<td>200 mg</td>
</tr>
<tr>
<td><em>(standardized to contain 5% gingerol)</em></td>
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</tr>
<tr>
<td>Quercetin</td>
<td>75 mg</td>
</tr>
<tr>
<td>Rutin</td>
<td>75 mg</td>
</tr>
<tr>
<td>Rosemary Extract <em>(Rosmarinus officinalis)(leaf)</em></td>
<td>50 mg</td>
</tr>
<tr>
<td><em>(standardized to contain 7% carnosic acid)</em></td>
<td></td>
</tr>
<tr>
<td>Trans Resveratrol</td>
<td>5 mg</td>
</tr>
<tr>
<td><em>(from 10 mg Polygonum cuspidatum (root)</em></td>
<td></td>
</tr>
</tbody>
</table>

*Daily Value not established.
Natural Agents Provide Balance

Increased Dietary AA

FEWER Side Effects, LESS OA

JOURNAL OF MEDICINAL FOOD
J Med Food 10 (3) 2007, 442–451
Antioxidant, genomic activity of flavocoxid

- **Regulatory Proteins and mRNA:**
  - p38 ↓
  - JUNK ↓
  - NFκB ↓
  - IκBα ↑ (regulates NFκB activation)

- **Cytokine mRNA and Protein:**
  - IL-1β ↓
  - IL-6 ↓
  - TNFα ↓

- **Enzyme mRNA and Protein:**
  - COX-2 ↓ (celecoxib and ibuprofen increase COX-2)
  - 5-LOX ↓
  - iNOS ↓

All of these proteins are involved in a variety of chronic diseases including osteoarthritis.

Burnett et al., 2007
Altavilla et al., 2009
Messina et al., 2009
Tseng-Crank et al., 2008, 2010
Polito et al., 2010
Burnett et al., 2011
NSAIDs vs. Flavocoxid

Mediators of Inflammation
Volume 2011, Article ID 385780, 11 pages

Higher Side Effects

COX-1, COX-2

Lower Side Effects

PLA_2, COX-1, COX-2, 5-LOX, NF_{\kappa}B, JNK, p38, reactive oxygen species, cytokines
CNS Motor Dysfunction

• Rehabilitative exercises; spinal stabilization
• ADL training
• Balance and proprioceptive training
• Restoration of the normal “software program” in the cerebellum and motor system
Patients with Widespread Pain and Fatigue

Differential Diagnosis into Subsets

- Classic FMS
- Metabolic-Functional
- Medical-Pathologic
- Musculo-Skeletal

Complete medical exam and management of the pathology that is causing the pain and fatigue.

- Limbic system over-activity.
- Sleep disorder must be treated.
- Anxiety, depression, PTSD?
- Psychotropic meds may be needed per MD.
- Cog Behav Therapy, Biofeedback

- Exam to determine the NMS pain generator(s).
- Chiropractic manual techniques, massage, rehab, modalities, etc.
- Ortho, neuro, or physical medicine referral.

- Exam to find what metabolic dysfunction is causing the pain and fatigue.
- Vitamin or enzyme deficiency?
- Functional hormone imbalance?
- Food allergies, GI dysbiosis, toxicity, meds?
The Great FMS Masqueraders/Imposters

- Sub-optimal thyroid function

- Myofascial pain syndrome

- Sub-optimal mitochondrial/Energy metabolism

*Based on my opinion from clinical experience and discussion with colleagues who also manage a large number of patients presenting with the FMS label.*
Patient presents with Sx of widespread pain & fatigue

Is pain pattern truly the "widespread pain" of FMS

Is there frank joint swelling?

Lab tests to rule out arthritides:
- Lyme Disease
- RA
- Lupus, Gout, Ank Spond, etc.

Does this "regional pain" indicate a musculoskeletal referred pain pattern?

Suspicion of visceral referred pain requires complete medical evaluation.
Go to Box 1

Musculoskeletal disorders: Determine pain generator(s) and render appropriate treatment.

Patient may have pathology or disease that requires medical management

Screen for functional and metabolic disorders

Strong likelihood for Classic FMS. Patient needs a team approach:

Note 1: Classic FMS
1. True widespread allodynia or hyperalgesia.
2. Significant sleep disorder.
3. History of significant anxiety/depression/PTSD.
4. Fatigue/ neuroendocrine disorders.

Note 2: Overlapping Disorders
1. Having one disorder does not mutually exclude other disorders, as patients may have an overlap between disorders.
2. Many patients with psychological illnesses and internal disorders have poor nutrition and would benefit from metabolic therapies.
3. Many patients with psychological illnesses have concurrent myofascial trigger points that would benefit from soft tissue therapies.

Box 1
Full physical exam, medical history, and blood/urine tests:

Tests positive?

Does patient exhibit all aspects of Classic FMS?

^See Note 1

Tests negative?

Patient presents with Sx of widespread pain & fatigue

Is pain pattern truly the "widespread pain" of FMS

Is there frank joint swelling?

Lab tests to rule out arthritides:
- Lyme Disease
- RA
- Lupus, Gout, Ank Spond, etc.

Does this "regional pain" indicate a musculoskeletal referred pain pattern?

Suspicion of visceral referred pain requires complete medical evaluation.
Go to Box 1

Musculoskeletal disorders: Determine pain generator(s) and render appropriate treatment.

Patient may have pathology or disease that requires medical management

Screen for functional and metabolic disorders

Strong likelihood for Classic FMS. Patient needs a team approach:

Note 1: Classic FMS
1. True widespread allodynia or hyperalgesia.
2. Significant sleep disorder.
3. History of significant anxiety/depression/PTSD.
4. Fatigue/ neuroendocrine disorders.

Note 2: Overlapping Disorders
1. Having one disorder does not mutually exclude other disorders, as patients may have an overlap between disorders.
2. Many patients with psychological illnesses and internal disorders have poor nutrition and would benefit from metabolic therapies.
3. Many patients with psychological illnesses have concurrent myofascial trigger points that would benefit from soft tissue therapies.
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