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References:

This book uses pubmed extensively and uses an condensed notation consisting of:

- Hyperlink to PubMed article (Year of Publication)
- **JCFS**: JOURNAL OF CHRONIC FATIGUE SYNDROME

An astrophe "*" after the year of publication indicates that the full article is available for free.

High rates of autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome and atopic diseases among women with endometriosis: a survey analysis.

<http://www.ncbi.nlm.nih.gov/pubmed/12351553>

A cross-sectional survey was conducted in 1998 by the Endometriosis Association of 3680 USA members with surgically diagnosed endometriosis. Almost all responders had pain (99%), and many reported infertility (41%). Compared with published rates in the general USA female population, women with endometriosis had higher rates of hypothyroidism (9.6 versus 1.5%, $P < 0.0001$), fibromyalgia (5.9 versus 3.4%, $P < 0.0001$), chronic fatigue syndrome (4.6 versus 0.03%, $P < 0.0001$), rheumatoid arthritis (1.8 versus 1.2%, $P = 0.001$), systemic lupus erythematosus (0.8 versus 0.04%, $P < 0.0001$), Sjögren's syndrome (0.6 versus 0.03%, $P < 0.0001$) and multiple sclerosis (0.5 versus 0.07%, $P < 0.0001$), but not hyperthyroidism or diabetes. Allergies and asthma were more common among women with endometriosis alone (61%, $P < 0.001$ and 12%, $P < 0.001$ respectively) and highest in those with fibromyalgia or chronic fatigue syndrome (88%, $P < 0.001$ and 25%, $P < 0.001$ respectively) than in the USA female population (18%, $P < 0.001$ and 5%, $P < 0.001$ respectively).

2 Introduction

In 2012, more than one article was published every day on Chronic Fatigue Syndrome¹ with over 5700 articles listed on the National Library of Medicine. The NLM has over 2400 full text articles and 140 online books citing CFS.

3 The many subsets of Chronic Fatigue Syndrome

Many definitions of Chronic Fatigue Syndrome have been created in an attempt to research this family of conditions. Historically, they are based on the collection of symptoms seen with more recent work

¹ <http://www.ncbi.nlm.nih.gov/pubmed?term=Chronic%20Fatigue%20Syndrome>

pointing to symptoms and patients genes being related. Depending on which definition is being used, CFS affects from 0.006% to 3% of the population^{2 3}.

- “All patients fulfilled the criteria for CFS as described by Sharpe et al. (J R Soc Med 1991; 84: 118-21), only 18 patients (20.5%) fulfilled the CDC criteria.”⁴
- “Patients with ME had significantly higher scores on concentration difficulties and a subjective experience of infection, and higher levels of IL-1, TNF α , and neopterin than patients with CFS.”
 - “ME/CFS patients should be subdivided into ME (with Post-Exertional Malaise - PEM) and CFS (without PEM).”⁵
- In one sample of CFS patients⁶, we had
 - ~ 50% meeting the 1988 and 1994 definitions.
 - ~ 20% meeting the 1994 definition only.
 - ~ 30% not meeting either definition.
- A recent study⁷ found that over 10 years:
 - ~ 20% had an different illness
 - ~ 4% went into remission
 - ~ 8% went into reduced symptoms
 - ~ 67% still had it.
- A study over 25 years⁸:
 - 20% maintained a CFS diagnosis
 - 80% continued to be impaired in functionality and symptoms severity 74%

3.1.1 Comorbid Conditions:

A recent study found significant overlap with fibromyalgia, irritable bowel syndrome, migraine headaches, sensory hypersensitivity (dyspnea; congestion; rhinorrhea)⁹.

	CFS Alone	With MCS	With FM	With MCS and FM
Sample population A ¹⁰	44%	24%	16%	17%
Depression	Less			More

² <http://www.ncbi.nlm.nih.gov/pubmed/19445810> (2008)

³ <http://www.ncbi.nlm.nih.gov/pubmed/12562565> (2003)

⁴ <http://www.ncbi.nlm.nih.gov/pubmed/7738491> (1995)

⁵ <http://www.ncbi.nlm.nih.gov/pubmed/22521895> (2012)

⁶ <http://www.ncbi.nlm.nih.gov/pubmed/10721210> (1999)

⁷ <http://www.ncbi.nlm.nih.gov/pubmed/21401284> (2011)

⁸ <http://www.ncbi.nlm.nih.gov/pubmed/22753044> (2012)

⁹ <http://www.ncbi.nlm.nih.gov/pubmed/20615318> (2010)

¹⁰ <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1890280/?tool=pmcentrez> (2007)

Sleep Quality	Less		More
Fatigue		More	Less
Pain	Least		More
Sample population B ¹¹	35%	41%	16%

Other studies have reported:

- 70% of FM has CFS¹²
 - 58% of females
 - 80% of males
- 35-70% of CFS has FM¹³
- IBS¹⁴:
 - 92% of CFS
 - 77% of FM
 - 64% of Temporomandibular disorder (TMD)
- Temporomandibular disorder (TMD)
 - 18%¹⁵-52%¹⁶ has FM
- 70%¹⁷ of FM have Temporomandibular disorder
- 41%¹⁸ - 67%¹⁹ of CFS has MCS
- Gender distribution for Chronic Lyme Disease matches that of FM and CFS²⁰
 - 10-20% of Lyme disease become chronic Lyme disease²¹

3.1.2 Multiple Chemical Sensitivity

3.1.3 Postural Tachycardia Syndrome

Postural tachycardia syndrome (POTS) have significant overlap with CFS^{22 23 24 25} and FM^{26 27}. It is closely related to orthostatic intolerance. CFS patients with POTS have greater orthostatic tachycardia²⁸ and neurocognitive impairment²⁹. POTS is also seen with traumatic brain injury^{30 31} and electrical injury^{32 33}.

¹¹ <http://www.ncbi.nlm.nih.gov/pubmed/11020095> (2000)

¹² <http://www.ncbi.nlm.nih.gov/pubmed/14743240> (2004 *)

¹³ <http://www.ncbi.nlm.nih.gov/pubmed/14743240> (2004 *)

¹⁴ <http://www.ncbi.nlm.nih.gov/pubmed/10647761> (2000)

¹⁵ <http://www.ncbi.nlm.nih.gov/pubmed/8923373> (1996)

¹⁶ <http://www.ncbi.nlm.nih.gov/pubmed/17096090> (2007)

¹⁷ <http://www.ncbi.nlm.nih.gov/pubmed/8923373> (1996)

¹⁸ <http://www.ncbi.nlm.nih.gov/pubmed/11020095> (2000)

¹⁹ <http://www.ncbi.nlm.nih.gov/pubmed/9167975> (1997 *)

²⁰ <http://www.ncbi.nlm.nih.gov/pubmed/19514824> (2009)

²¹ <http://www.cdc.gov/lyme/postLDS/index.html>

²² <http://www.ncbi.nlm.nih.gov/pubmed/21906029> (2012 *)

²³ <http://www.ncbi.nlm.nih.gov/pubmed/18091356> (2008)

1. Temporomandibular disorder

- Associations of polymorphic genes, related to folates, SHMT, MTHFD and MTR, oxidative stress GSTM1 and neurotransmission DRD4, with TMD³⁴

3.2 Related Conditions

3.2.1 Autoimmune Disease Interstitial Pneumonia

This was first seen with the onset of interstitial pneumonia spread in Nagoya, Japan in 1995 with 313 chronic pneumonia patients³⁵

- Deemed the same^{36 37}
- Recurrence of active form pneumonia was seen³⁸

3.2.2 Phosphate Diabetes

This present with similar symptoms; one study found that 10% of CFS patients had been misdiagnosed and had phosphate diabetes³⁹.

3.2.3 Macrophagic myofasciitis

This condition was first reported in 1998 and is associated with aluminum hydroxide in various vaccines. The syndrome that meets both Center for Disease Control and Oxford criteria for the so-called chronic fatigue syndrome in about half of patients⁴⁰.

3.2.4 Gulf War Illness

Gulf war illness exhibits similar characteristics. The cause may be a macrophagic myofasciitis like condition.

²⁴ <http://www.ncbi.nlm.nih.gov/pubmed/18805903> (2008)

²⁵ <http://www.ncbi.nlm.nih.gov/pubmed/21919887> (2012)

²⁶ <http://www.ncbi.nlm.nih.gov/pubmed/19007537> (2008)

²⁷ <http://www.ncbi.nlm.nih.gov/pubmed/19890437> (2008)

²⁸ <http://www.ncbi.nlm.nih.gov/pubmed/21906029> (2012 *)

²⁹ <http://www.ncbi.nlm.nih.gov/pubmed/21919887> (2012 *)

³⁰ <http://www.ncbi.nlm.nih.gov/pubmed/20865679> (2010 *)

³¹ <http://www.ncbi.nlm.nih.gov/pubmed/22143364> (2011)

³² <http://www.ncbi.nlm.nih.gov/pubmed/20015131> (2010)

³³ <http://www.ncbi.nlm.nih.gov/pubmed/17669092> (2007)

³⁴ <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3129576/?tool=pmcentrez> (2011)

³⁵ <http://www.ncbi.nlm.nih.gov/pubmed/8986468> (1996)

³⁶ <http://www.ncbi.nlm.nih.gov/pubmed/16634532> (2006)

³⁷ <http://www.ncbi.nlm.nih.gov/pubmed/15583836> (2005)

³⁸ <http://www.ncbi.nlm.nih.gov/pubmed/15583836> (2005)

³⁹ <http://www.ncbi.nlm.nih.gov/pubmed/9683977> (1998)

⁴⁰ <http://www.ncbi.nlm.nih.gov/pubmed/12660567> (2003)

3.2.5 Ciguatera poisoning

In some cases, symptoms are matches for other conditions, for example, chronic ciguatera fish poisoning^{41 42} which exhibits similar symptoms and laboratory manifestations⁴³.

3.2.6 Traumatic Brain Injury

CFS has been described by some as disease caused brain injury. Brain infection and injury can result in over production of cytokines including TNF-alpha ⁴⁴. TNF-alpha is produced by glia in the brain^{45 46} and the appropriate level is required for the correct operation of the brain.

Fatigue level was significantly correlated⁴⁷ with the following three factors:

- 55% have poor sleep quality
- 36% have anxiety disorders
- 65% have vitamin-D deficiency

⁴¹ <http://www.ncbi.nlm.nih.gov/pubmed/12784262> (2003)

⁴² <http://www.ncbi.nlm.nih.gov/pubmed/18348309> (2008)

⁴³ <http://www.ncbi.nlm.nih.gov/pubmed/11327394> (2001)

⁴⁴ <http://www.ncbi.nlm.nih.gov/pubmed/22749718> (2012)

⁴⁵ <http://www.ncbi.nlm.nih.gov/pubmed/11910117> (2002)

⁴⁶ <http://www.ncbi.nlm.nih.gov/pubmed/16547515> (2006)

⁴⁷ <http://www.ncbi.nlm.nih.gov/pubmed/22190008> (2011)

4 My History with CFS

4.1 1973 – Onset without PEM

In the 1960's I attended high school and was selected for a special enrichment program called Berg Science Seminars, I placed in the top three of National Mathematics competitions and placed well in International competitions.

In 1973 I was attending University, I started doing triple honors in Mathematics, Chemistry, Physics. Towards the end of my 3rd year, I suffered a major cognitive collapse.

4.2 1999 – Onset with PEM

4.3 2012 – Onset with PEM initially

5 Pathogen and CFS

CFS has a pattern similar to Chicken Pox caused by varicella zoster virus(VZV)⁴⁸ a member of the herpes family. Reactivation of VZV occurs as herpes zoster⁴⁹ (i.e., shingles) and postherpetic neuralgia⁵⁰. A pathogen causes an initial acute sickness and can return later with different symptoms when reactivated. The duration of the reactivation is much longer than the acute period and can become persistent. Unlike Chicken Pox the pathogens for CFS are both viral and bacterial. This type of infection is termed an occult or asymptomatic infection in older literature. The infection stays latent until something causes it to be activated.

Often CFS happens after a flu like illness (34%⁵¹)

5.1 Probable Pathogens

Historically, there has been a holy quest for *the* infection that causes CFS. In 1998, David Berg who ran a lab specializing in coagulation testing noted that several MDs mentioned their patients while being treated for infertility with low dosage heparin -- reported that their CFS symptom disappeared. Berg conducted some studies and found that a high percentage of CFS patients were hyper coagulated (thick blood) with a high percentage having a *coagulation defect*. He proposed that CFS was a variation⁵² of antiphospholipid antibody syndrome(APS) also known as Hughes Syndrome. Subsequently, searches for *the* pathogen, multiple studies finding high incidences of certain infections in CFS, and APS came together. Pathogens causing APS and pathogens associated with CFS were effectively the identical list as

⁴⁸ http://en.wikipedia.org/wiki/Varicella_zoster_virus

⁴⁹ http://en.wikipedia.org/wiki/Herpes_zoster

⁵⁰ http://en.wikipedia.org/wiki/Postherpetic_neuralgia

⁵¹ <http://www.ncbi.nlm.nih.gov/pubmed/1648795> (1991)

⁵² <http://www.ncbi.nlm.nih.gov/pubmed/10695770> Full Text: <http://www.wisconsinhyperbarics.com/research-pdf/ChronicFatigue443.pdf>

shown in the table below. For many of the infections listed below, the rates seen in CFS patients vary between 8% and 36%⁵³.

The impact on research for the pathogen associated with CFS is significant: if you are testing for one specific pathogen of eight likely candidates – you may find in a CFS sample only 1/8 having the infection while your control groups may be 1/50. A naïve conclusion is that this pathogen may be associated with CFS but is not the cause. This wrong conclusion comes from the wrong assumption that there is *one* pathogen responsible instead of a family of pathogens (both viral and bacterial). Researchers have postulated that since rickettsial microorganisms are ubiquitous in human populations they and the human species normally live in peaceful coexistence. In rare cases, for unknown reasons, varieties of them may become aggressive and pathogenic⁵⁴. One study found 31% of CFS patients had two different infections, and 22% had three different infections⁵⁵ (leaving just 47% with one infection). A different study found just 17% had multiple infections^{56 57}. In 2010, a paper entitled Microbial infections in eight genomic subtypes of chronic fatigue syndrome/myalgic encephalomyelitis⁵⁸, found subsets of specific genes for CFS and associated infections⁵⁹. Ongoing studies of genes are in progress⁶⁰. CFS may in time be sub-classed on a *person's genes* and the *associated infection* to those genes. There is also the appearance that antigenic complexes or immunomodulatory complexes persist in higher levels for an extended period(12+ yrs) despite no infection being present⁶¹. Infection DNA was still detectable after 5 years⁶². Infection having a reserve in bone marrow (65%⁶³ of patients) has been implicated⁶⁴.

⁵³ <http://www.ncbi.nlm.nih.gov/pubmed/7856214> (1994)

⁵⁴ <http://www.ncbi.nlm.nih.gov/pubmed/19269110> (2009)

⁵⁵ <http://www.ncbi.nlm.nih.gov/pubmed/10691196> (1999)

⁵⁶ <http://www.ncbi.nlm.nih.gov/pubmed/12423773> (2002)

⁵⁷ <http://www.ncbi.nlm.nih.gov/pubmed/14743240> (2004 *)

⁵⁸ <http://www.ncbi.nlm.nih.gov/pubmed/19955554> (2010), full text:

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921262/?tool=pubmed>

⁵⁹ <http://www.ncbi.nlm.nih.gov/pubmed/16316396> (2005)

⁶⁰ <http://www.ncbi.nlm.nih.gov/pubmed/21964398> (2011)

⁶¹ <http://www.ncbi.nlm.nih.gov/pubmed/20639288> (2010 *)

⁶² <http://www.ncbi.nlm.nih.gov/pubmed/19556396> (2009 *)

⁶³ <http://www.ncbi.nlm.nih.gov/pubmed/10982079> (2000)

⁶⁴ <http://www.ncbi.nlm.nih.gov/pubmed/15625349> (2005) for Coxiella Burnetii. Also reported for Mycoplasma.

Chronic Fatigue Syndrome Associated Infections	APS Infections ⁶⁵
EBV ^{66 67 68 69 70 71} (20% ⁷² -23% ⁷³ - 57% ⁷⁴)	Epstein-Bar Virus (EBV)
VZV ^{75 76}	Varicella zoster virus (VZV -chicken pox)
**	Human Immunodeficiency virus (HIV)
HHV6 ^{77 78 79} (31% ⁸⁰)	Human Herpes Virus 6 (HHV6)
CMV ^{81 82 83}	Cytomegalovirus (CMV) (HHV6)
Coxiella burnetii ^{84 85} Enterovirus ⁸⁶ (13%-27% ⁸⁷)	Coxiella burnetii (Enterovirus)
Lyme ^{88 89}	Lyme Disease (Rickettsia)
	Mediterranean spotted fever (Rickettsia)
Mycoplasma ⁹⁰ (50% ⁹¹ - 52% ⁹² - 69% ^{93 94 95})	Mycoplasma

⁶⁵ "Hughes Syndrome Antiphospholipid Syndrome" Springer, 2000 (2nd printing 2002), editor M.A. Khamashta. Chapter 14, "Infections and Antiphospholipid Syndrome"(by A.E. Gharavi and S.S. Pierangeli), p. 135

⁶⁶ <http://www.ncbi.nlm.nih.gov/pubmed/3033337> (1987)

⁶⁷ <http://www.ncbi.nlm.nih.gov/pubmed/1850540> (1991)

⁶⁸ <http://www.ncbi.nlm.nih.gov/pubmed/8730646> (1996)

⁶⁹ <http://www.ncbi.nlm.nih.gov/pubmed/21415952> (2010)

⁷⁰ <http://www.ncbi.nlm.nih.gov/pubmed/19955554> (2010)

⁷¹ <http://www.ncbi.nlm.nih.gov/pubmed/1850542> (1991)

⁷² <http://www.ncbi.nlm.nih.gov/pubmed/14554250> (2003)

⁷³ <http://www.ncbi.nlm.nih.gov/pubmed/1648795> (1991)

⁷⁴ <http://www.ncbi.nlm.nih.gov/pubmed/15113035> (2004)

⁷⁵ <http://www.ncbi.nlm.nih.gov/pubmed/19520522> (2009)

⁷⁶ <http://www.ncbi.nlm.nih.gov/pubmed/15175170> (2004)

⁷⁷ <http://www.ncbi.nlm.nih.gov/pubmed/15175170> (2004)

⁷⁸ <http://www.ncbi.nlm.nih.gov/pubmed/8993762> (1996)

⁷⁹ <http://www.ncbi.nlm.nih.gov/pubmed/1850542> (1991)

⁸⁰ <http://www.ncbi.nlm.nih.gov/pubmed/12887507> (2003)

⁸¹ <http://www.ncbi.nlm.nih.gov/pubmed/6093268> (1984)

⁸² <http://www.ncbi.nlm.nih.gov/pubmed/8234851> (1993)

⁸³ <http://www.ncbi.nlm.nih.gov/pubmed/12182109> (2002)

⁸⁴ <http://www.ncbi.nlm.nih.gov/pubmed/16978917> (2006)

⁸⁵ <http://www.ncbi.nlm.nih.gov/pubmed/12145392> (2002 *)

⁸⁶ <http://www.ncbi.nlm.nih.gov/pubmed/17872383> (2008)

⁸⁷ <http://www.ncbi.nlm.nih.gov/pubmed/14554250> (2003)

⁸⁸ <http://www.ncbi.nlm.nih.gov/pubmed/21383843> (2011)

⁸⁹ <http://www.ncbi.nlm.nih.gov/pubmed/9362985> (1997)

⁹⁰ <http://www.ncbi.nlm.nih.gov/pubmed/14743240> (2004)

⁹¹ <http://www.ncbi.nlm.nih.gov/pubmed/12879275> (2003)

⁹² <http://www.ncbi.nlm.nih.gov/pubmed/12887507> (2003)

⁹³ <http://www.ncbi.nlm.nih.gov/pubmed/12423773> (2002)

Anecdotal ⁹⁶	Leprosy
**	Tuberculosis
**	Syphilis
Parvovirus B ^{97 98 99}	Parvovirus B
**	Hepatitis
Chlamydia pneumoniae ^{100(8%¹⁰¹)}	Chlamydia pneumoniae ^{102 103 104}

** indicate that fatigue is seen and because of the prior acute infection, the fatigue is not of *unknown origin*.

Table 1 APS and CFS Infections compared

A recent study also implicates the following gram-negative infections¹⁰⁵:

- Hafnia Alvei¹⁰⁶ – a member of Enterobacteriaceae
- Pseudomonas Aeruginosa¹⁰⁷
- Morganella Morganii¹⁰⁸ – a member of Enterobacteriaceae
- Pseudomonas Putida¹⁰⁹
- Citrobacter Koseri¹¹⁰ – a member of Enterobacteriaceae
- Klebsiella pneumoniae¹¹¹ – a member of Enterobacteriaceae

The Ross River virus¹¹² has also been implicated.

⁹⁴ <http://www.ncbi.nlm.nih.gov/pubmed/9778455> (1998)

⁹⁵ <http://www.ncbi.nlm.nih.gov/pubmed/9879928> (1998)

⁹⁶ I have met and talked with a person who came down with CFS after being treated successfully for leprosy.

⁹⁷ <http://www.ncbi.nlm.nih.gov/pubmed/19955554> (2010)

⁹⁸ <http://www.ncbi.nlm.nih.gov/pubmed/20007355> (2010)

⁹⁹ <http://www.ncbi.nlm.nih.gov/pubmed/19414405> (2009)

¹⁰⁰ <http://www.ncbi.nlm.nih.gov/pubmed/17561687> (2007)

¹⁰¹ <http://www.ncbi.nlm.nih.gov/pubmed/12887507> (2003)

¹⁰² <http://www.ncbi.nlm.nih.gov/pubmed/15847779> (2005)

¹⁰³ <http://www.ncbi.nlm.nih.gov/pubmed/10737040> (1999)

¹⁰⁴ <http://www.ncbi.nlm.nih.gov/pubmed/18190881> (2008)

¹⁰⁵ <http://www.ncbi.nlm.nih.gov/pubmed/19112401> (2008)

¹⁰⁶ <http://de.wikipedia.org/wiki/Hafnia>

¹⁰⁷ http://en.wikipedia.org/wiki/Pseudomonas_aeruginosa

¹⁰⁸ http://en.wikipedia.org/wiki/Morganella_morganii

¹⁰⁹ http://en.wikipedia.org/wiki/Pseudomonas_putida

¹¹⁰ http://en.wikipedia.org/wiki/Citrobacter_koseri

¹¹¹ http://en.wikipedia.org/wiki/Klebsiella_pneumoniae

¹¹² <http://www.ncbi.nlm.nih.gov/pubmed/21964398> (2011) http://en.wikipedia.org/wiki/Ross_River_Virus

These opportunistic infections are known to be resistant to multiple antibiotics (aminoglycosides, fluoroquinolones, tetracyclines, chloram-phenicol, and sulfamethoxazole-trimethoprim¹¹³). They also prefer low oxygen environments.

¹¹³ http://www.medscape.com/viewarticle/409761_4

5.1.1 CFS Pathogens as Immune System Tricksters

In a 2012 New Scientist article¹¹⁴, two of the above pathogens (EVV,CMV) exhibit the ability to cause T-cells trained to recognize this pathogen – to fail to recognize the infection subsequently¹¹⁵. This may explain the difference of appearance between the initial acute presentation of a pathogen and the subsequent occult presentation with different apparent symptoms (just like VZV). This behavior may be a characteristic of all of the CFS associated pathogens.

5.1.2 Pathogens persistence

Since 1944 it has been known that antibiotic-tolerant bacteria existed. These bacteria are not antibiotic-resistant mutants^{116 117} produced by the overuse of antibiotics. There exists a small fraction of essentially invulnerable cells. Bacterial populations produce persisters, cells that neither grow nor die in the presence of bactericidal agents, and thus exhibit multidrug tolerance¹¹⁸. In bacteria, persisters are dormant cells¹¹⁹ that may activate when conditions are right. Persister cells cause chronic infections¹²⁰. Antibiotics interfere with reproduction of active cells¹²¹; persisters sleep through the antibiotic attacks. Additional ways that bacteria resist antibiotics includes mutation, phenotypic variations and by forming biofilms¹²². Other studies implicate multiple pathways for persister formation, including energy production, the stringent response, global regulators, the trans-translation pathway, proteasomal protein degradation, toxin-antitoxin modules, and transporter or efflux mechanisms¹²³.

- Lyme produces antibiotic-tolerant persisters¹²⁴
- Candida produces antifungal-tolerant persisters¹²⁵
- These cells arose in the population at approximately 0.05% density under inhibitory conditions of antimicrobial compounds¹²⁶

Recent mathematical modeling of this resistance found:

“We find that constant dosing is not the optimal method for disinfection. Rather, cycling between application and withdrawal of the antibiotic yields the fastest killing of the bacteria.”¹²⁷

It has been suggested that a bacterial subpopulation becomes 'inoculates' against antibiotics by activating stress responses, leading to persister formation¹²⁸.

¹¹⁴ **New Scientist**, Vol. 214, No. 2870, June 23, 2012. P. 6-7

¹¹⁵

¹¹⁶ <http://www.ncbi.nlm.nih.gov/pubmed/19179767> (2008 *)

¹¹⁷ <http://www.ncbi.nlm.nih.gov/pubmed/17215163> (2007)

¹¹⁸ <http://www.ncbi.nlm.nih.gov/pubmed/15807669> (2005 *)

¹¹⁹ <http://www.ncbi.nlm.nih.gov/pubmed/16923951> (2006)

¹²⁰ <http://www.ncbi.nlm.nih.gov/pubmed/22221537> (2012)

¹²¹ <http://www.ncbi.nlm.nih.gov/pubmed/18453274> (2008)

¹²² <http://www.ncbi.nlm.nih.gov/pubmed/22751538> (2012)

• ¹²³ <http://www.ncbi.nlm.nih.gov/pubmed/22391538> (2012)

¹²⁴ <http://www.ncbi.nlm.nih.gov/pubmed/22253822> (2012)

¹²⁵ <http://www.ncbi.nlm.nih.gov/pubmed/16923951> (2006)

¹²⁶ <http://www.ncbi.nlm.nih.gov/pubmed/22730126> (2012)

¹²⁷ <http://www.ncbi.nlm.nih.gov/pubmed/22751538> (2012)

“Bacterial populations produce a small number of dormant persister cells that exhibit multidrug tolerance. All resistance mechanisms do essentially the same thing: prevent the antibiotic from hitting a target. By contrast, tolerance apparently works by shutting down the targets. Bactericidal antibiotics kill bacteria by corrupting their targets, rather than merely inhibiting them. Shutting down the targets then protects from killing. The number of persisters in a growing population of bacteria rises at mid-log and reaches a maximum of approximately 1% at stationary state. Similarly, slow-growing biofilms produce substantial numbers of persisters. The ability of a biofilm to limit the access of the immune system components, and the ability of persisters to sustain an antibiotic attack could then account for the recalcitrance of such infections in vivo and for their relapsing nature.” <http://www.ncbi.nlm.nih.gov/pubmed/18453274>

5.1.3 Biofilms

Biofilms are mini-cities of pathogens that have created city walls to defeat antibiotics by keeping them away from the inner inhabitants. 60% to 85% of all microbial infections involve biofilms¹²⁹. Most, if not all, bacteria (and fungi) are capable of forming biofilms¹³⁰. Microorganisms growing in a biofilm are highly resistant to antimicrobial agents by one or more mechanisms¹³¹. The main characteristics are:

- the increased resistance to antimicrobials¹³²;
- the protection of cells against the host's defense mechanisms¹³³
- cause chronic infections¹³⁴
- increased level of mutations¹³⁵
- NAC has been effective against them¹³⁶

The following mechanisms are likely connected with chronic/latent/occult infections¹³⁷:

- The failure of antibiotic penetration into the depth of a mature biofilm due to the biofilm matrix;
- The accumulation of high levels of antibiotic degrading enzymes;
- In the depth of biofilm, cells are experiencing nutrient limitation entering in a slow-growing or starved state; slow-growing or non-growing cells being not highly susceptible to antimicrobial agents, this phenomenon could be amplified by the presence of phenotypic variants or "persisters" and
- Biofilm's bacteria can turn on stress-response genes and switch to more tolerant phenotypes on exposure to environmental stresses;
- Genetic changes, probably selected by different stress conditions, such as mutations and gene transfer could occur inside the biofilm.

¹²⁸ <http://www.ncbi.nlm.nih.gov/pubmed/22426114> (2012)

¹²⁹ <http://www.ncbi.nlm.nih.gov/pubmed/21434589> (2010)

¹³⁰ <http://www.ncbi.nlm.nih.gov/pubmed/21485309> (2011)

¹³¹ <http://www.ncbi.nlm.nih.gov/pubmed/11932229> (2002)

¹³² <http://www.ncbi.nlm.nih.gov/pubmed/21497662> (2011)

¹³³ <http://www.ncbi.nlm.nih.gov/pubmed/21497662> (2011)

¹³⁴ <http://www.ncbi.nlm.nih.gov/pubmed/20149602> (2010)

¹³⁵ <http://www.ncbi.nlm.nih.gov/pubmed/20149602> (2010)

¹³⁶ <http://www.ncbi.nlm.nih.gov/pubmed/22650647> (2012)

¹³⁷ <http://www.ncbi.nlm.nih.gov/pubmed/21434589> (2010)

Recently identified foods that may impact biofilms are horseradish¹³⁸ and garlic¹³⁹.

5.1.4 The internal flora dimension

A common co-morbid syndrome with CFS is Irritable Bowel Syndrome (IBS). Recently there have been anecdotal reports of CFS remission occurring during long-term treatment of IBS with rifaximin¹⁴⁰. Since Rifaximin¹⁴¹ does not enter the blood system but does alter internal flora, it suggests that internal flora may play a significant role. There have been reports of CFS remission caused by fecal transplants¹⁴².

This raises the question whether CFS antibiotic protocols acts solely on the infection, but may also alter internal flora in a desirable way. Most CFS antibiotics use members of the tetracycline family of antibiotics which are also anticoagulants^{143 144}.

5.2 CFS Pathogens and Onset

The diagram below shows the typical the typical onset of CFS patients. The key is some event that impacts the immune system ability to keep latent infections controlled. The two most common triggers are stress and a flu-like illness (which may actually be flu!). Stress as a trigger is also seen with VZV (shingles). EBV levels increases with stress¹⁴⁵. For some of the CFS associated infections, epinephrine (adrenaline) increases the growth rate significantly^{146 147} resulting in a double whammy: more growth of the bacteria and less immune response.

At this point, a genetic or acquired aspect is added to the mix: a coagulation defect. The infection triggers coagulation which normally is removed by the body. The quantity of coagulation triggered and the amount that the body can remove are out of balance.

5.3 Infections and cytokines production:

- Chlamydia and Mycoplasma pneumonia increases: IL6, IFN-gamma, TNF-alpha¹⁴⁸.
- Mycoplasma pneumonia increases: IL6,IL10 and TNF=alpha¹⁴⁹
- Mycoplasma pneumonia toxins increases: IL4, IL13 (30x), CCL17, CCL22 (70x)¹⁵⁰
- Parvovirus B19 increases IL-4, IL-6, IL-8, TNF-alpha, IFN-gamma, MCP-1, GM-CSF, TGF-beta 1, and endothelin-1 (ET-1)¹⁵¹.

¹³⁸ <http://www.ncbi.nlm.nih.gov/pubmed/22286987> (2012)

¹³⁹ <http://www.ncbi.nlm.nih.gov/pubmed/15716452> (2005)

¹⁴⁰ <http://www.ncbi.nlm.nih.gov/pubmed/22045120> (2012)

¹⁴¹ <http://en.wikipedia.org/wiki/Rifaximin>

¹⁴² <http://www.the-scientist.com/news/display/57795/#ixzz1MXtBRu9S>

¹⁴³ <http://www.ncbi.nlm.nih.gov/pubmed/7446537> (1980)

¹⁴⁴ <http://www.ncbi.nlm.nih.gov/pubmed/1421670> (1992)

¹⁴⁵ <http://www.ncbi.nlm.nih.gov/pubmed/22229027> (2011)

¹⁴⁶ <http://www.ncbi.nlm.nih.gov/pubmed/11125844> (2000)

¹⁴⁷ <http://www.ncbi.nlm.nih.gov/pubmed/1731173> (1992)

¹⁴⁸ <http://www.ncbi.nlm.nih.gov/pubmed/9730797> (1998)

¹⁴⁹ <http://www.ncbi.nlm.nih.gov/pubmed/22000436> (2011)

¹⁵⁰ <http://www.ncbi.nlm.nih.gov/pubmed/22281984> (2012)

¹⁵¹ <http://www.ncbi.nlm.nih.gov/pubmed/15258981> (2004)

Speculation: the decrease may be due to exhaustion or starvation of the cytokines producers.

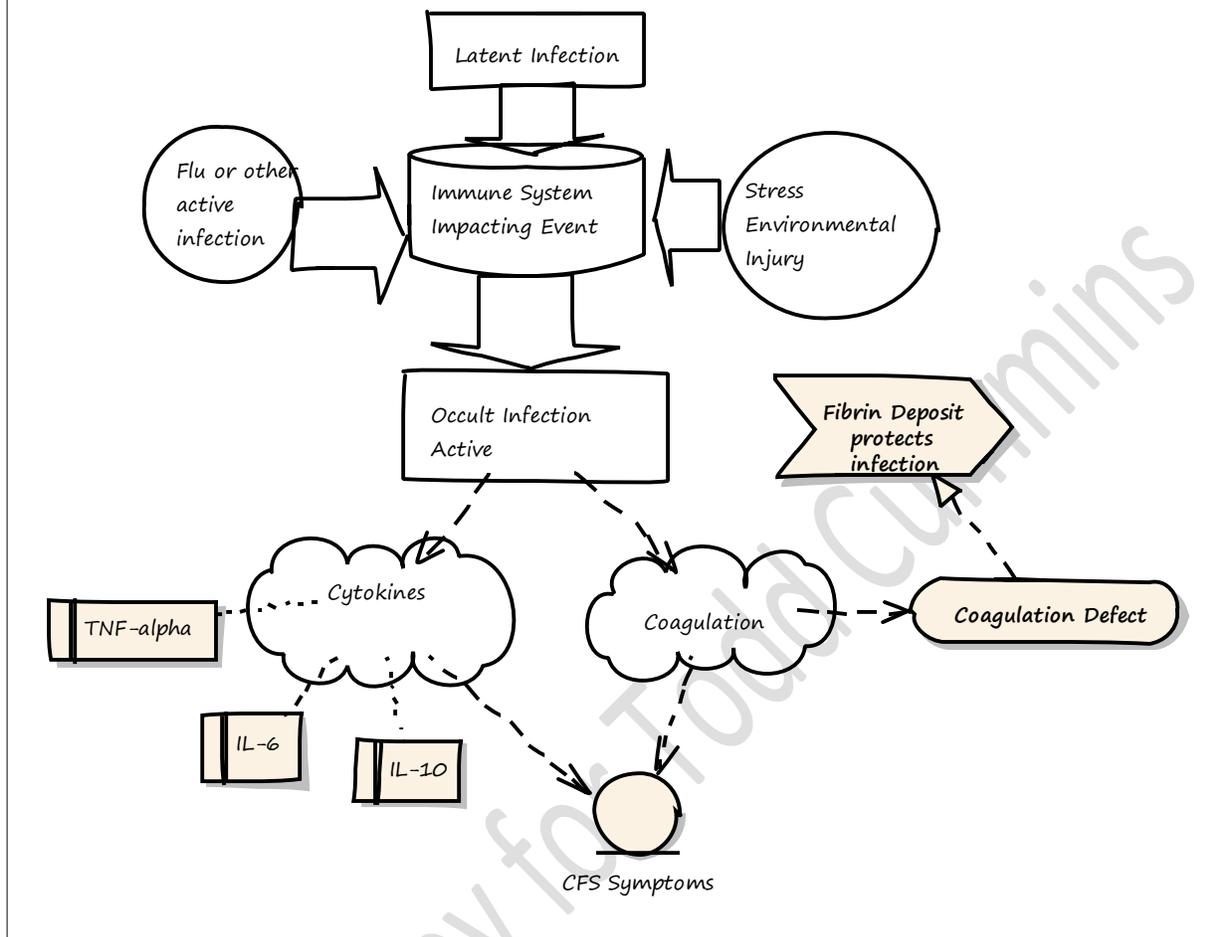
Cytokines inhibitors and removers

One of the key aspect of any thing that reduced cytokine levels is whether is removes the cytokine or reduces the production of the cytokine. In the case of TNF-alpha we read

“TNF-alpha mRNA is rapidly produced in response to brain ischemia within 1 h, reaches a peak at 6-12 h post ischemia, and subsides 1-2 days later.”¹⁵²

So if some medication reduces the production of cytokines, there may no apparent immediate effect and the impact may not be seen until 72 hours later. Similarly if the medication clears in a few hours and is stopped for a day, it may take 3 days or more before the prior status returns.

¹⁵² <http://ukpmc.ac.uk/abstract/MED/7880718/reload=0;jsessionid=XvjgujppquKbq5RBuCDDeP.0>



This results in a neuroinflammatory condition which may not have a simple one-to-one causality. For example, high IL-6 levels results in neurological disorders¹⁵³ (high IL-6 levels are also seen after strokes¹⁵⁴). At the same time, coagulation may result in hypoxia (oxygen starvation) which can result in significant changes of behavior and mood swings. Similarly, high TNF-alpha is associated with sleep problems¹⁵⁵ as well as impacting wakefulness regulation¹⁵⁶; hypoxia produces similar sleep disturbances.

¹⁵³ <http://www.ncbi.nlm.nih.gov/pubmed/22345884> (2012)

¹⁵⁴ <http://www.ncbi.nlm.nih.gov/pubmed/22425021> (2012) <http://www.ncbi.nlm.nih.gov/pubmed/19404547> (2009)

¹⁵⁵ <http://www.ncbi.nlm.nih.gov/pubmed/22003330> (2011)

¹⁵⁶ <http://www.ncbi.nlm.nih.gov/pubmed/22706407> (2012)

EBV

EBV has exhibit changes of cytokines similar to that seen in CFS, with increased production of TNF-alpha, IL-1beta, IL-6, IL-8, and IL-10¹⁵⁷.

- Causes coagulation¹⁵⁸

6 Treatment Protocols

If we are dealing with a bacterial pathogen, then returning the pathogen to a latent state is possible through the use of antibiotics. The question arises: which antibiotics, for how long, etc.

The most mature protocol is known through Cecile Jadin, a surgeon in South Africa. She did not invent or discover the protocol – simply remember it from the work of her father and Nobel Prize winner, , on tropical infections. The protocol assumes that there will be *antibiotic resistance* to a single antibiotic, and uses multiple rotating antibiotics to eliminate the infection.

6.1 Symptom Relief

6.1.1 Graded Exercise Therapy

GET can reduce fatigue and improve physical functioning in some patients¹⁵⁹. Qigong exercise improved symptoms¹⁶⁰. Exercise is identified by C. Jadin as an essential part of her antibiotic protocol.

6.1.2 Cognitive-Behavioral Therapy

CBT can impact cytokines, for example, reduce IL1-beta, IL-8¹⁶¹ but not IL-6, TNF-alpha¹⁶². CBT can reduce fatigue and improve physical functioning in some patients¹⁶³. It can reverse some of the low grey matter volume in the brain¹⁶⁴. Some view it as harmful¹⁶⁵ and recent studies found no or little significant efficacy^{166 167 168}.

¹⁵⁷ <http://www.ncbi.nlm.nih.gov/pubmed/15664781> (2005)

¹⁵⁸ <http://www.ncbi.nlm.nih.gov/pubmed/5125284> (1971)

¹⁵⁹ <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2907931/?tool=pubmed> (2008)

¹⁶⁰ <http://www.ncbi.nlm.nih.gov/pubmed/22736201> (2012)

¹⁶¹ <http://www.ncbi.nlm.nih.gov/pubmed/21654719> (2011)

¹⁶² <http://www.ncbi.nlm.nih.gov/pubmed/18511165> (2008)

¹⁶³ <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2907931/?tool=pubmed> (2008)

¹⁶⁴ <http://www.ncbi.nlm.nih.gov/pubmed/18587150> (2008)

¹⁶⁵ <http://www.ncbi.nlm.nih.gov/pubmed/19855350> (2009)

¹⁶⁶ <http://www.ncbi.nlm.nih.gov/pubmed/19855351> (2009)

¹⁶⁷ <http://www.ncbi.nlm.nih.gov/pubmed/17014748> (2006 *)

¹⁶⁸ <http://www.ncbi.nlm.nih.gov/pubmed/17853290> (2008)

6.2 Remission

6.2.1 Anticoagulant Treatment

The protocol¹⁶⁹ proposed by Dave Berg, of Hemex Lab in 2000, consists of anti-pathogens and anticoagulants. Berg has since retired and Hemex has been purchased by a larger company.

Treatment	Start	End
Heparin (4-5000 units BID)	Day 1	Day 180
Transfer Factor (3 capsules/day)	Day 30	Day 120
Bromelain (500 – 1000 mg/day)	Day 1	Day 120
Antibiotics (left to MD)	Day 30	Day 120

6.2.2 Antibiotic Studies

Past publications/conference proceedings reported a high (> 50%) remission rate with the use of antibiotics. The following are pub-med articles dealing with CFS or chronic-related-pathogens experiences using antibiotics. For example, "Chronic Lyme disease" is a vaguely defined term that has been applied to patients with unexplained prolonged subjective symptoms, whether or not there was or is evidence of *B. burgdorferi* infection¹⁷⁰. Often CFS is seen after an acute onset of an infection that was apparently treated successfully. One study found that if the acute onset was accompanied by stress, that the incidence of developing CFS was much higher.

- Med Hypotheses. 2009 Jun;72(6):736-9. Epub 2009 Mar 6. On the question of infectious aetiologies for multiple sclerosis, schizophrenia and the **chronic fatigue syndrome and their treatment with antibiotics**¹⁷¹. Frykholm BO.
- Excellent results that persisted for at least a year after 60 days of antibiotics [2 patients]
- *Chronic fatigue syndrome after Q fever*¹⁷²
 - Fluoroquinolones and Tetracyclines for 3-12 months, [2/3 recovered]
- *Treatment of chronic fatigue syndrome with antibiotics: pilot study assessing the involvement of Coxiella burnetii infection*¹⁷³

¹⁶⁹ http://gordonresearch.com/articles_fibromyalgia/cfs-fm_treatment_hemex.html (2000)

¹⁷⁰ <http://www.ncbi.nlm.nih.gov/pubmed/19514824> (2009)

¹⁷¹ <http://www.ncbi.nlm.nih.gov/pubmed/19269110> (2009)

¹⁷² <http://www.ncbi.nlm.nih.gov/pubmed/17599032> (2007)

- minocycline or doxycycline for 3 months
 - Prior Q-Fever CFS (54 patients) improved.
 - No Q-Fever CFS (4 patients) no change.
- *Improvement of chronic nonspecific symptoms by long-term minocycline treatment in Japanese patients with Coxiella burnetii infection considered to have post-Q fever fatigue syndrome*¹⁷⁴.
 - Minocycline (100mg/day) for 3 months, all patients improved.
- *Mycoplasma blood infection in chronic fatigue and fibromyalgia syndromes*¹⁷⁵
 - Long term doxycycline – most patients go into remission.
- *Benefits and harms of doxycycline treatment for Gulf War veterans' illnesses: a randomized, double-blind, placebo-controlled trial*¹⁷⁶.
 - Long-term treatment with doxycycline (200mg/day) did not improve outcomes of GWVIs at 1 year.
- *Counterpoint: long-term antibiotic therapy improves persistent symptoms associated with Lyme disease*¹⁷⁷
 - prolonged antibiotic therapy (duration, >4 weeks) may be beneficial for patients with persistent Lyme disease symptoms
- Lyme disease: point/counterpoint¹⁷⁸
 - The optimal antibiotic regimen for chronic Lyme disease remains to be determined.
- Standardised in vitro susceptibility testing of Borrelia burgdorferi against well-known and newly developed antimicrobial agents--possible implications for new therapeutic approaches to Lyme disease¹⁷⁹
 - beta-lactams, macrolides, tetracyclines, fluoroquinolones, evernimomycins, and the ketolide family of antimicrobial agents show enhanced in vitro activity against borrelia.
- Controlled trials of antibiotic treatment in patients with post-treatment chronic Lyme disease¹⁸⁰
 - Treatment using a single antibiotic have not been successful¹⁸¹ (typically ceftriaxone, possibly with a repeat the antibiotic used for Lyme originally)^{182 183 184 185}
- **Cecile Jadin** (South African MD - surgeon: gerinjadin@icon.co.za) official sites: <http://cecilejadin.com/> <http://chronicfatiguesyndrome.co.za/case-studies> , <http://drcjadin.com/>, protocol
 - Vibromycin 100 or 200 depending on weight and tolerance
 - Riostaine – f(oxy)tetracycline) 250 QID, 500 TDS, 500 QTD
 - Minomycin 50mg plus 100mg bd or 100 bd plus Rulide (Macrolide 150mg.)

¹⁷³ <http://www.ncbi.nlm.nih.gov/pubmed/16415546> (2005)

¹⁷⁴ <http://www.ncbi.nlm.nih.gov/pubmed/14964579> (2004)

¹⁷⁵ <http://www.ncbi.nlm.nih.gov/pubmed/12879275> (2003)

¹⁷⁶ <http://www.ncbi.nlm.nih.gov/pubmed/15262663> (2004)

¹⁷⁷ <http://www.ncbi.nlm.nih.gov/pubmed/17578772> (2007)

¹⁷⁸ <http://www.ncbi.nlm.nih.gov/pubmed/15918774> (2005)

¹⁷⁹ <http://www.ncbi.nlm.nih.gov/pubmed/12141737> (2002)

¹⁸⁰ <http://www.ncbi.nlm.nih.gov/pubmed/12804167> (2002)

¹⁸¹ <http://www.cdc.gov/lyme/diagnostictreatment/Treatment/prolonged/index.html>

¹⁸² <http://www.ncbi.nlm.nih.gov/pubmed/12821734> (2003)

¹⁸³ <http://www.ncbi.nlm.nih.gov/pubmed/12821733> (2003)

¹⁸⁴ <http://www.ncbi.nlm.nih.gov/pubmed/11450676> (2001)

¹⁸⁵ <http://www.ncbi.nlm.nih.gov/pubmed/12804167> (2002)

- Tetralisal (lymecycline) – 300mg bd X 7 days plus flagy Metronidazole 200mg bd 400bd
- Dumoxin 100mg + 50mg daily 100mg bd plus Quinolone =Ciprobay 500mp bd or Maxs wuin BD
- Dalacin C 150mg or 2 X 4 7 days each treatment to be taken with inteflora (no milk products)

6.3 Gut Flora Altering

In the last 2 years there has been a wave of interesting findings on gut-flora and autoimmune illnesses. Irritable bowel syndrome is *very often comorbid* with chronic fatigue syndrome.

"As director of the Centre for Digestive Diseases in New South Wales, Borody oversees five to six fecal transplants a week, most of which are for patients with irritable bowel syndrome. But occasionally, he treats patients that, in addition to bowel complaints, also have seemingly non-gut related conditions such as **chronic fatigue syndrome**, acne, and multiple sclerosis. And he's getting some early evidence that, in some cases, the transplant can reverse the symptoms of those accompanying conditions as well. "

<http://www.the-scientist.com/news/display/57795/#ixzz1MXTBRu9S>

Also <http://www.ncbi.nlm.nih.gov/pubmed/15220681>

An alternative to fecal transplants is Rifamycin.

"Rifaximin is a nonsystemic antibiotic that has shown efficacy in IBS"

- <http://www.ncbi.nlm.nih.gov/pubmed/22251066> Expert Opin Pharmacother. 2012 Feb;13(3):433-40. Epub 2012 Jan 18. Rifaximin for the treatment of irritable bowel syndrome. Cremonini F, Lembo A. Source Harvard Medical School

" Rifaximin inhibits a broad spectrum of bacteria in the bile-rich small bowel and susceptible bacteria in the aqueous colon, and alters microbial virulence and epithelial cell function. The different mechanisms of action of rifaximin potentially explain the use of the drug in widely varied diseases and syndromes."

- <http://www.ncbi.nlm.nih.gov/pubmed/21226639> Expert Opin Pharmacother. 2011 Feb;12(2):293-302. Biologic properties and clinical uses of rifaximin. DuPont HL.
- <http://www.ncbi.nlm.nih.gov/pubmed/22180705> World J Gastroenterol. 2011 Nov 14;17(42):4643-6. Rifaximin in the treatment of inflammatory bowel disease. Guslandi M.
- <http://www.ncbi.nlm.nih.gov/pubmed/21407187> Am J Gastroenterol. 2011 Apr;106(4):661-73. Epub 2011 Mar 15. Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. Khan KJ, Ullman TA, Ford AC, Abreu MT, Abadir A, Marshall JK, Talley NJ, Moayyedi P. McMaster University Medical Centre

“We demonstrated that rifaximin, while not altering the overall structure of the human colonic microbiota, increased bifidobacteria and led to variation of metabolic profiles associated with potential beneficial effects on the host.”

- <http://www.ncbi.nlm.nih.gov/pubmed/20852272> J Antimicrob Chemother. 2010 Dec;65(12):2556-65. Epub 2010 Sep 18. Rifaximin modulates the colonic microbiota of patients with Crohn's disease: an in vitro approach using a continuous culture colonic model system. Maccaferri S, Vitali B, Klinder A, Kolida S, Ndagijimana M, Laghi L, Calanni F, Brigidi P, Gibson GR, Costabile A.

The Effect of a Nonabsorbed Oral Antibiotic (Rifaximin) on the Symptoms of the Irritable Bowel Syndrome http://www.rima.org/web/medline_pdf/Annals_2006-Colon-irritable.pdf

Gut. 2011 May;60(5):631-7. Epub 2011 Jan 5. Dysbiosis of the faecal microbiota in patients with Crohn's disease and their unaffected relatives. [Joossens M](#), [Huys G](#), [Cnockaert M](#), [De Preter V](#), [Verbeke K](#), [Rutgeerts P](#), [Vandamme P](#), [Vermeire S](#). Department of Gastroenterology, University Hospital Gasthuisberg, Leuven, Belgium. <http://www.ncbi.nlm.nih.gov/pubmed/21209126>

“Unaffected relatives of patients with CD have a different composition of their microbiota compared with healthy controls. This dysbiosis is not characterised by lack of butyrate producing-bacteria as observed in CD but suggests a role for microorganisms with mucin degradation capacity.”

<http://www.ncbi.nlm.nih.gov/pubmed/20848492>

Less seen in Crohns

- Dialister invisus
- Faecalibacterium prausnitzii (increases with Rifaximin)
- Bifidobacterium adolescentis (increases with Rifaximin)
- Eubacterium rectale
- Bacteroides fragilis, vulgatus
- Ruminococcus albus, R. callidus, R. bromii

INCREASE

- Ruminococcus gnavus
- Enterococcus sp.,
- Clostridium difficile,
- Escherichia coli,
- Shigella flexneri,
- Listeria sp

6.3.1 Animals with CFS and their Physicians

CFS is seen in animals and in vets. Both have been successfully treated by arsenic-based drugs.

- Eight birds of Prey report¹⁸⁶
- Cats and dogs^{187 188}
- Horses¹⁸⁹
- Veterinary surgeon and wife¹⁹⁰

I have been unable to find any follow up studies on this approach.

6.3.2 Chemotherapy for CFS

In 2011, I received a phone call from a CFS friend because her CFS suddenly disappeared while undergoing chemotherapy and she wanted to know if I knew anything about it. I did, I meet with another CFS person in Reno, NV, that also went into remission with chemotherapy in 2003. In reading through a 2012 CFS/ME Conference report¹⁹¹, similar remissions have been reported in Norway¹⁹².

7 Living with CFS

Immune function decreases over time with CFS¹⁹³ suggesting increased susceptibility to pathogens – especially similar pathogens. One way of viewing this may be immune system exhaust from being active for so long. Nichol's research found ...

8 Laboratory Manifestation

In preparing this book, I happened to revisit the US Social Security page on Chronic Fatigue Syndrome and noted that it had two clinical aspects that reflect the knowledge of the time:

- *Presence of EBV* – this is just one of at least a dozen infections
- *MRI Scans* – inconsistent findings in subsequent studies and unreliable for diagnostic purposes.

One important factor to remember is that all of the differences found are based on the average of the study group. A positive or negative result on any one measure cannot be used to infer CFS or not-CFS.

¹⁸⁶ <http://www.ncbi.nlm.nih.gov/pubmed/15129582> (2001)

¹⁸⁷ <http://www.ncbi.nlm.nih.gov/pubmed/11440190> (2001)

¹⁸⁸ <http://www.ncbi.nlm.nih.gov/pubmed/12688127> (2003)

¹⁸⁹ <http://www.ncbi.nlm.nih.gov/pubmed/11131041> (2001)

¹⁹⁰ <http://www.ncbi.nlm.nih.gov/pubmed/11561958> (2001)

¹⁹¹

<http://www.investinme.org/Documents/Journals/Journal%20of%20liME%20Vol%206%20Issue%201%20Screen.pdf>

¹⁹² <http://www.ncbi.nlm.nih.gov/pubmed/19566965> (2009)

¹⁹³ <http://www.ncbi.nlm.nih.gov/pubmed/22571715> (2012 *)

The better studies will report statistical significance which means that A and B are statistically associated. This does not mean that A causes B or B causes A. It is likely true that “People that drive late model Volkswagen Passat have a higher life expectancy than people driving older pickups”. The reasons may include education and income levels:

- One group has the money to buy a new Passat, eat healthier food, see MDs more often.
- The other group has less money, eat cheap high-fat food, and often not covered by medical insurance.

Medical history is full of cases where there is a push to reduce A in the belief that it will reduce B. B is not reduced, instead, some unexpected factor C is eventually identified that impacts A and B.

It is human nature to deal with the unknown to try gaining control by allowing partial facts to become standing belief. A few simple examples of myth and reality are shown below.

CFS Patients	Reality
Have magnesium deficiency	45% ¹⁹⁴ - 50% ¹⁹⁵ of CFS patients have low levels
Are low in CoQ 10	45% ¹⁹⁶ of CFS patients have low levels
Have high levels of cytokines	40% ¹⁹⁷ of CFS patients do not have high levels of the typical 9 cytokines.

- “Overall, serum markers of inflammation and immune activation are of limited diagnostic usefulness in the evaluation of patients with CSF ...”¹⁹⁸
- “was significantly higher than that in healthy controls (14.5 +/- 1.0 pg/mL, p = 0.02). However, there was a wide range of values in the CFS group.”¹⁹⁹

1. Aldosterone

- Lower in CFS patients²⁰⁰
- No difference²⁰¹

8.1 Alpha-MSH

Alpha-melanocyte-stimulating hormone are peptide hormones that are produced by cells in the intermediate lobe of the pituitary gland.

- High levels in the 1st 5 years of CFS, declines afterwards, wide variation of levels²⁰².

¹⁹⁴ <http://www.ncbi.nlm.nih.gov/pubmed/9513929> (1997)

¹⁹⁵ <http://www.ncbi.nlm.nih.gov/pubmed/10872900> (2000)

¹⁹⁶ <http://www.ncbi.nlm.nih.gov/pubmed/20010505> (2009)

¹⁹⁷ <http://www.ncbi.nlm.nih.gov/pubmed/8148443> (1994)

¹⁹⁸ <http://www.ncbi.nlm.nih.gov/pubmed/9034999> (1997)

¹⁹⁹ <http://www.ncbi.nlm.nih.gov/pubmed/20731841> (2010)

²⁰⁰ <http://www.ncbi.nlm.nih.gov/pubmed/17851136> (2007)

²⁰¹ <http://www.ncbi.nlm.nih.gov/pubmed/20199497> (2010)

- Low levels seen with Sick Building Syndrome^{203 204}

8.2 Beta 2-Microglobulin

It is higher on average in CFS patients than controls²⁰⁵. Beta-2 microglobulin is associated with high viral loads²⁰⁶.

8.3 Blood

- Objectively measured abnormalities of blood pressure variability in CFS²⁰⁷
- Lower blood pressure in sleep²⁰⁸
- Lower blood pressure²⁰⁹
- Less and slower variability of blood pressure^{210 211}
- Lower total blood volume²¹² (8% - 9%²¹³ - 15%²¹⁴ less), plasma volume (13%²¹⁵) and red blood cell volume (19%)^{216 217 218}.
- 35% lower peak oxygen consumption²¹⁹
- Significant decrease in red cell distribution width²²⁰
- Higher percentages of misshaped red blood cells²²¹
 - Impaired capillary blood flow.
 - Changed red cell shape populations
 - High values for flat blood-cells

8.3.1 Red Blood Count

8.4 CD4/CD8 Ratio

- Abnormal²²²

²⁰² <http://www.ncbi.nlm.nih.gov/pubmed/20731841> (2010)

²⁰³ <http://www.ncbi.nlm.nih.gov/pubmed/17010568> (2006)

²⁰⁴ <http://www.ncbi.nlm.nih.gov/pubmed/15681119> (2005)

²⁰⁵ <http://www.ncbi.nlm.nih.gov/pubmed/9034999> (1997)

²⁰⁶ <http://www.ncbi.nlm.nih.gov/pubmed/11365017> (1998)

²⁰⁷ <http://www.ncbi.nlm.nih.gov/pubmed/22670061> (2012)

²⁰⁸ <http://www.ncbi.nlm.nih.gov/pubmed/21059182> (2011)

²⁰⁹ <http://www.ncbi.nlm.nih.gov/pubmed/19297309> (2009)

²¹⁰ <http://www.ncbi.nlm.nih.gov/pubmed/22670061> (2012)

²¹¹ <http://www.ncbi.nlm.nih.gov/pubmed/20890710> (2011)

²¹² <http://www.ncbi.nlm.nih.gov/pubmed/19534728> (2009)

²¹³ <http://www.ncbi.nlm.nih.gov/pubmed/11748048> (2002 *)

²¹⁴ <http://www.ncbi.nlm.nih.gov/pubmed/19469714> (2009)

²¹⁵ <http://www.ncbi.nlm.nih.gov/pubmed/19469714> (2009)

²¹⁶ <http://www.ncbi.nlm.nih.gov/pubmed/19469714> (2009)

²¹⁷ <http://www.ncbi.nlm.nih.gov/pubmed/10910366> (2000)

²¹⁸ <http://www.ncbi.nlm.nih.gov/pubmed/17720950> (2007)

²¹⁹ <http://www.ncbi.nlm.nih.gov/pubmed/11748048> (2002 *)

²²⁰ <http://www.ncbi.nlm.nih.gov/pubmed/17720950> (2007 *)

²²¹ <http://orthomolecular.org/library/jom/2001/pdf/2001-v16n03-p157.pdf>

- Elevated ratio^{223 224}
 - Seen to increase with EBV load²²⁵
- Decreased with HHV6 and HHV7²²⁶

8.5 Choline

- Relatively high in occipital cortex²²⁷
- Abnormally high^{228 229 230}
- Improves with viral clearance²³¹, resulting in significant improvements in verbal learning, memory, and visuo-spatial memory.
- Tumeric (curcumin) normalizes^{232 233}.
- Lipoic Acid normalizes²³⁴.

8.6 Citicoline

Cytidine diphosphate-choline believed to help with recover of neurological issues.

- Not found effective in a large study^{235 236}
- Effective when given within 24 hrs of trauma²³⁷
- Possesses a substantial neuroregenerative potential²³⁸
- Potential as an adjunct therapy in the treatment of infectious diseases²³⁹.

8.7 Circadian Rhythm

- No evidence of disturbance^{240 241}

8.8 Coagulation

- No evidence of increased platelet activation²⁴².
- Increases in mean platelet volume²⁴³

²²² <http://www.ncbi.nlm.nih.gov/pubmed/11327394> (2001)

²²³ <http://www.ncbi.nlm.nih.gov/pubmed/1850542> (1991)

²²⁴ <http://www.ncbi.nlm.nih.gov/pubmed/15345193> (2004)

²²⁵ <http://www.ncbi.nlm.nih.gov/pubmed/22764883> (2012)

²²⁶ <http://www.ncbi.nlm.nih.gov/pubmed/17276369> (2006)

²²⁷ <http://www.ncbi.nlm.nih.gov/pubmed/12197861> (2002)

²²⁸ <http://www.ncbi.nlm.nih.gov/pubmed/10761837> (2000)

²²⁹ <http://www.ncbi.nlm.nih.gov/pubmed/15253888> (2004)

²³⁰ <http://www.ncbi.nlm.nih.gov/pubmed/12598734> (2003)

²³¹ <http://www.ncbi.nlm.nih.gov/pubmed/22027578> (2012)

²³² <http://www.ncbi.nlm.nih.gov/pubmed/21839772> (2011)

²³³ <http://www.ncbi.nlm.nih.gov/pubmed/20637830> (2011)

²³⁴ <http://www.ncbi.nlm.nih.gov/pubmed/18655815> (2008)

²³⁵ <http://www.ncbi.nlm.nih.gov/pubmed/22691567> (2012)

²³⁶ <http://www.ncbi.nlm.nih.gov/pubmed/12468781> (2002) - original study

²³⁷ <http://www.ncbi.nlm.nih.gov/pubmed/22732142> (2012)

²³⁸ <http://www.ncbi.nlm.nih.gov/pubmed/22581817> (2012)

²³⁹ <http://www.ncbi.nlm.nih.gov/pubmed/19401146> (2009)

²⁴⁰ <http://www.ncbi.nlm.nih.gov/pubmed/21532961> (2011)

²⁴¹ <http://www.ncbi.nlm.nih.gov/pubmed/11238482> (2001)

²⁴² <http://www.ncbi.nlm.nih.gov/pubmed/16479189> (2006)

- Low level coagulation activation²⁴⁴
- Found hypercoagulable state suggests that symptoms may be due to poor blood flow²⁴⁵

8.9 Cortisol

- No difference found^{246 247 248 249 250}
- Low in 33% of CFS patients²⁵¹
- Salivary cortisone lower²⁵²
- Higher in evening²⁵³ and morning²⁵⁴
- Improvement from 5 - 15 mg of cortisol²⁵⁵.
- No difference from placebo²⁵⁶

8.10 Cyclo-oxygenase-2

Cyclo-oxygenase-2 (COX-2)

- Higher in CFS patients^{257 258}
- Reduces with Grape Seed Extract

8.11 Cytokines

Different studies^{259 260 261 262 263 264 265 266} have found slightly different results for cytokines in CFS. The table below Table 2 Cytokines changes seen in Chronic Fatigue Syndrome is my aggregation of these studies. Factors such as type of onset, post-exercise time and co-morbidity to related syndromes are

²⁴³ <http://www.ncbi.nlm.nih.gov/pubmed/17720950> (2007 *)

²⁴⁴ <http://www.ncbi.nlm.nih.gov/pubmed/10695770> (1999)

²⁴⁵ <http://www.ncbi.nlm.nih.gov/pubmed/11085289> (2000)

²⁴⁶ <http://www.ncbi.nlm.nih.gov/pubmed/21532961> (2011 *)

²⁴⁷ <http://www.ncbi.nlm.nih.gov/pubmed/15922454> (2005)

²⁴⁸ <http://www.ncbi.nlm.nih.gov/pubmed/16868267> (2006)

²⁴⁹ <http://www.ncbi.nlm.nih.gov/pubmed/20199497> (2010)

²⁵⁰ <http://www.ncbi.nlm.nih.gov/pubmed/15730417> (2005)

²⁵¹ <http://www.ncbi.nlm.nih.gov/pubmed/11722149> (2001)

²⁵² <http://www.ncbi.nlm.nih.gov/pubmed/15922454> (2005)

²⁵³ <http://www.ncbi.nlm.nih.gov/pubmed/21682138> (2011)

²⁵⁴ <http://www.ncbi.nlm.nih.gov/pubmed/18378875> (2008 *)

²⁵⁵ JCFs. Vol 14:3 (2008) Diagnosis and Treatment of Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysfunction in Patients with Chronic Fatigue Syndrome (CFS) and Fibromyalgia (FM)

²⁵⁶ <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2907931/> (2008)

²⁵⁷ <http://www.ncbi.nlm.nih.gov/pubmed/19127706> (2009)

²⁵⁸ <http://www.ncbi.nlm.nih.gov/pubmed/17693978> (2007)

²⁵⁹ <http://www.ncbi.nlm.nih.gov/pubmed/21619669> (2011)

²⁶⁰ <http://www.ncbi.nlm.nih.gov/pubmed/20230500> (2010)

²⁶¹ <http://www.ncbi.nlm.nih.gov/pubmed/19909538> (2009 *)

²⁶² <http://www.ncbi.nlm.nih.gov/pubmed/19647494> (2009)

²⁶³ <http://www.ncbi.nlm.nih.gov/pubmed/21967891> (2012)

²⁶⁴ <http://www.ncbi.nlm.nih.gov/pubmed/11327394> (2001)

²⁶⁵ <http://www.ncbi.nlm.nih.gov/pubmed/17543146> (2007)

²⁶⁶ <http://www.ncbi.nlm.nih.gov/pubmed/12508404> (2003)

suspected to cause some of the variations. The accuracy of the tests has improved significantly in the last decade, so newer results should be preferred over older results.

40% of CFS patients may have none of these – they are not definitive, as this quotation implies:

*“60% of patients had elevated levels of one or more of the nine soluble immune mediators tested.”*²⁶⁷

More recent research suggests that what is seen may be due to genetics -

*“inherited variability in cytokine responses may affect the likelihood of developing symptoms ...”*²⁶⁸

Table 2 Cytokines changes seen in Chronic Fatigue Syndrome

Increase	Decrease
IL-6	CD56(bright) NK cells
IL-10	NK and CD8(+) T cells
IFN-gamma,	NK phenotypes
BTTNF-alpha	CD40L
CD4(+)CD25(+) T cells	IL-8,
	IL-13
IL-1alpha	IL-15.
IL-1beta	
IL-4	
IL-5	
IL-13	
LT-alpha	

²⁶⁷ <http://www.ncbi.nlm.nih.gov/pubmed/8148443> (1994)

²⁶⁸ <http://www.ncbi.nlm.nih.gov/pubmed/14514772> (2003)

8.11.1 Cytokines impacts

Cytokines levels appear to match the symptoms seen in patients²⁶⁹, for example:

- IL-1beta: (low levels) pain , fatigue, depression, anxiety
- IL-10: (low) fatigue
- TNF-alpha(high): sleep problems²⁷⁰, depression²⁷¹
- IL-1beta, TNF-alpha, IL6 (high) cognitive issues^{272, 273}
- IL-10, IL-6, TNF-alpha(high): unusual fatigue, irritability, and feelings of demoralization²⁷⁴
- IL-6 (High): neurological disorders²⁷⁵
- IL-6 (High): impacts sleep, social isolation and physical ability
- CD56 NK cell activity and emotional reaction²⁷⁶
- IL-1beta, IL6, TNF-alpha impacts wakefulness regulation²⁷⁷

CFS has been described as infection causes brain injury. Similar cytokines changes are seen:

- IL-6 and IL-10 elevated after strokes²⁷⁸
- IL-1, IL-6, TNF-alpha after strokes²⁷⁹

The levels of cytokines appear to decrease over time²⁸⁰ resulting in some decreases of some symptoms.

8.12 C-Reactive Protein

C-reactive protein (CRP) is a protein found in the blood that is elevated in response to inflammation. It is higher on average in CFS patients than controls^{281 282}. High levels are associated with depression^{283 284 285} and sleep disorders²⁸⁷. The incidence of these symptoms appears to be genetic²⁸⁸.

- Therapy: See Boswellia Gum, Ginger

²⁶⁹ <http://www.ncbi.nlm.nih.gov/pubmed/22174319> (2011)

²⁷⁰ <http://www.ncbi.nlm.nih.gov/pubmed/22003330> (2011)

²⁷¹ <http://www.ncbi.nlm.nih.gov/pubmed/22180575> (2012)

²⁷² <http://www.ncbi.nlm.nih.gov/pubmed/21868631> (2011)

²⁷³ <http://www.ncbi.nlm.nih.gov/pubmed/14561190> (2002)

²⁷⁴ <http://www.ncbi.nlm.nih.gov/pubmed/20484723> (2010)

²⁷⁵ <http://www.ncbi.nlm.nih.gov/pubmed/22345884> (2012)

²⁷⁶ <http://www.ncbi.nlm.nih.gov/pubmed/21585130> (2011)

²⁷⁷ <http://www.ncbi.nlm.nih.gov/pubmed/22706407> (2012)

²⁷⁸ <http://www.ncbi.nlm.nih.gov/pubmed/22425021> (2012)

²⁷⁹ <http://www.ncbi.nlm.nih.gov/pubmed/19404547> (2009)

²⁸⁰ <http://www.ncbi.nlm.nih.gov/pubmed/22571715> (2012 *)

²⁸¹ <http://www.ncbi.nlm.nih.gov/pubmed/9034999> (1997)

²⁸² <http://www.ncbi.nlm.nih.gov/pubmed/18031285> (2008)

²⁸³ <http://www.ncbi.nlm.nih.gov/pubmed/19111923> (2009)

²⁸⁴ <http://www.ncbi.nlm.nih.gov/pubmed/22716910> (2012)

²⁸⁵ <http://www.ncbi.nlm.nih.gov/pubmed/22429274> (2012)

²⁸⁶ <http://www.ncbi.nlm.nih.gov/pubmed/22180575> (2012)

²⁸⁷ <http://www.ncbi.nlm.nih.gov/pubmed/22518315> (2012)

²⁸⁸ <http://www.ncbi.nlm.nih.gov/pubmed/22580182> (2012)

8.13 Galantamine

An Alzheimer drug tried to address cognitive issues.

- Not effective²⁸⁹

8.14 Glutamine

A non-essential amino acid.

- Significant reduced, as well as ornithine (another amino acid)²⁹⁰
- Reduced level associated with Magnesium deficiency²⁹¹
- Glutamine, N-acetyl cysteine and zinc in combination improves symptoms²⁹²

8.15 Heart

- Increased heart Rate^{293 294 295}, higher rates were more fatigued^{296 297}
- Reduced left ventricular mass (reduced by 23%), end-diastolic volume (30%), stroke volume (29%) and cardiac output (25%)²⁹⁸
- Reduced stroke (volume pumped)^{299 300}
- Smaller heart³⁰¹ (61%³⁰²)
- ECG Pattern³⁰³
- Tachycardia³⁰⁴ often seen
 - Especially with JHR³⁰⁵

8.16 Inducible NO synthase

Inducible NO synthase (iNOS) increases with IL-1beta, IL-6, TNF-alpha and IFN-gamma.

- Higher in CFS patients^{306 307 308}

²⁸⁹ <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2907931/?tool=pubmed> (2008)

²⁹⁰ <http://www.ncbi.nlm.nih.gov/pubmed/22728138> (2012)

²⁹¹ <http://www.ncbi.nlm.nih.gov/pubmed/10872900> (2000)

²⁹² <http://www.ncbi.nlm.nih.gov/pubmed/19112401> (2008)

²⁹³ <http://www.ncbi.nlm.nih.gov/pubmed/11528333> (2001)

²⁹⁴ <http://www.ncbi.nlm.nih.gov/pubmed/21059182> (2011)

²⁹⁵ <http://www.ncbi.nlm.nih.gov/pubmed/12357281> (2002)

²⁹⁶ <http://www.ncbi.nlm.nih.gov/pubmed/17851136> (2007)

²⁹⁷ <http://www.ncbi.nlm.nih.gov/pubmed/21382927> (2011)

²⁹⁸ <http://www.ncbi.nlm.nih.gov/pubmed/21793948> (2012)

²⁹⁹ <http://www.ncbi.nlm.nih.gov/pubmed/12357281> (2002)

³⁰⁰ <http://www.ncbi.nlm.nih.gov/pubmed/22120591> (2011)

³⁰¹ <http://www.ncbi.nlm.nih.gov/pubmed/22120591> (2011)

³⁰² <http://www.ncbi.nlm.nih.gov/pubmed/18636530> (2008)

³⁰³ <http://www.ncbi.nlm.nih.gov/pubmed/17851136> (2007)

³⁰⁴ <http://www.ncbi.nlm.nih.gov/pubmed/17630594> (2007)

³⁰⁵ See Jarisch-Herxheimers Reaction

³⁰⁶ <http://www.ncbi.nlm.nih.gov/pubmed/10790736> (2000)

³⁰⁷ <http://www.ncbi.nlm.nih.gov/pubmed/19127706> (2009)

³⁰⁸ <http://www.ncbi.nlm.nih.gov/pubmed/17693978> (2007)

- Not different³⁰⁹

8.17 Lysozyme

It is higher on average in CFS patients than controls³¹⁰.

8.17.1 Nexavir

8.18 N-acetyl cysteine

- Glutamine, N-acetyl cysteine and zinc in combination improves symptoms³¹¹

8.19 NFkappabeta

This is stimulated by TNF-alpha

- Higher in CFS patients than controls³¹².
- Higher in more severe CFS patients^{313 314}

8.20 Nicotinamide adenine dinucleotide

8.21 Neopterin

It is higher on average in CFS patients than controls^{315 316}.

8.22 Natural Killer (NK) Cell Subsets

This information is less reliable - data suggest that differences in controls from cluster and noncluster areas may be responsible for some of the inconsistencies in results from other studies³¹⁷

- No other significant differences of NK cell activity (CD3, CD4 and CD8) .
- No differences either in the number of leukocytes or in the number or percentage of lymphocytes, i.e. CD3, CD4, CD8 and CD19, could be found between CFS patients and the controls³¹⁸

There are some reported special cases:

³⁰⁹ <http://www.ncbi.nlm.nih.gov/pubmed/9824439> (1998)

³¹⁰ <http://www.ncbi.nlm.nih.gov/pubmed/21975140> (2011)

³¹¹ <http://www.ncbi.nlm.nih.gov/pubmed/19112401> (2008)

³¹² <http://www.ncbi.nlm.nih.gov/pubmed/17693979> (2007)

³¹³ <http://www.ncbi.nlm.nih.gov/pubmed/17693979> (2007)

³¹⁴ <http://www.ncbi.nlm.nih.gov/pubmed/17693978> (2007)

³¹⁵ <http://www.ncbi.nlm.nih.gov/pubmed/9034999> (1997)

³¹⁶ <http://www.ncbi.nlm.nih.gov/pubmed/21975140> (2011)

³¹⁷ <http://www.ncbi.nlm.nih.gov/pubmed/12717688> (2003)

³¹⁸ <http://www.ncbi.nlm.nih.gov/pubmed/17693977> (2007)

- CFS patients with active dual infection (Human Herpes Virus 6 & 7) were characterized by significant decrease of CD3+ and CD4+ T cells, significant increase of CD95+ cells and decrease of CD4+/CD8+ ratio.³¹⁹

8.23 Norepinephrine

- Higher norepinephrine levels^{320 321}

8.24 Plasma Osmolality

Plasma osmolality measures the body's electrolyte-water balance. It increases with dehydration and decreases with overhydration³²².

- Increased^{323 324}

8.25 Plasma Renin

Plasma Renin lays a major role in the body's regulation of blood pressure, thirst, and urine output³²⁵.

- Increased³²⁶
- Sodium Chloride (common salt) improved 50% of CFS patients³²⁷.

8.26 RNase-L

Proteolytic cleavage of the native RNase L enzyme is characteristic of the dysregulation of intracellular immunity in people with ME/CFS, but the origin of the dysregulation is speculative³²⁸.

8.27 Stress

- Stress + infection is a strong predictor for CFS³²⁹

8.28 Transforming Growth Factor – beta

- Elevated^{330 331 332 333 334 335}
- Inhibited by Kuibitang³³⁶, bojungikki-tang³³⁷ (herbs used in South Korea)

³¹⁹ <http://www.ncbi.nlm.nih.gov/pubmed/17276369> (2006)

³²⁰ <http://www.ncbi.nlm.nih.gov/pubmed/17851136> (2007)

³²¹ <http://www.ncbi.nlm.nih.gov/pubmed/10910366> (2000)

³²² http://en.wikipedia.org/wiki/Serum_osmolality

³²³ <http://www.ncbi.nlm.nih.gov/pubmed/20199497> (2010)

³²⁴ <http://www.ncbi.nlm.nih.gov/pubmed/8475696> (1993)

³²⁵ http://en.wikipedia.org/wiki/Plasma_renin_activity

³²⁶ <http://www.ncbi.nlm.nih.gov/pubmed/20199497> (2010)

³²⁷ <http://www.ncbi.nlm.nih.gov/pubmed/9292244> (1997)

³²⁸ <http://www.ncbi.nlm.nih.gov/pubmed/18269338> (2008)

³²⁹ <http://www.ncbi.nlm.nih.gov/pubmed/18419428> (2008)

³³⁰ <http://www.ncbi.nlm.nih.gov/pubmed/7496949> (1994)

³³¹ <http://www.ncbi.nlm.nih.gov/pubmed/1873478> (1991)

³³² <http://www.ncbi.nlm.nih.gov/pubmed/22118314> (2011)

³³³ <http://www.ncbi.nlm.nih.gov/pubmed/15808295> (2005)

³³⁴ <http://www.ncbi.nlm.nih.gov/pubmed/15280416> (2004)

³³⁵ <http://www.ncbi.nlm.nih.gov/pubmed/9083892> (1997)

8.29 Minerals - Metals

8.29.1 Aluminum

Aluminium oxyhydroxide (alum), a nanocrystalline compound forming agglomerates, has been used in vaccines for its immunological adjuvant effect since 1927. A small proportion of vaccinated people present with delayed onset of diffuse myalgia, chronic fatigue and cognitive dysfunction, and exhibit very long-term persistence of alum-loaded macrophages at the site of previous immunization, forming a granulomatous lesion called macrophagic myofasciitis (MMF)³³⁸.

- Higher with CFS^{339 340 341}
- Al is a potential factor for the induction of inflammation in Crohn's disease, and its immune activities share many characteristics with the immune pathology of Crohn's disease³⁴²
- Al concentration is associated with disturbed concentrations of essential metals, increased oxidative stress, and increased inflammation status³⁴³
- Known neurotoxic substance³⁴⁴
- Principal sources of Al intake from food contact materials are utensils made of Al and ceramic ware³⁴⁵.
 - Al concentration increased up to 2.6 mg/L after boiling tap water for 15 min in Al pans³⁴⁶
- Milk³⁴⁷:
 - Al concentration in bulk farm milk samples was found to be negligible.
 - Market milk revealed 65.0% of the examined samples were above the provisional acceptable permissible limits (PAPL).
 - 20% of the examined milk powder samples exceeded (PAPL)
 - Processed cheese wrapped in Al foil were significantly higher

8.29.1.1 Toxicity Treatment

- Done with [deferoxamine](#), a prescription drug. See <http://emedicine.medscape.com/article/165315-treatment>
- Or with EDTA.

³³⁶ <http://www.ncbi.nlm.nih.gov/pubmed/15013189> (2004)

³³⁷ <http://www.ncbi.nlm.nih.gov/pubmed/14686792> (2003)

³³⁸ <http://www.ncbi.nlm.nih.gov/pubmed/22235051> (2012)

³³⁹ <http://www.ncbi.nlm.nih.gov/pubmed/11470334> (2001)

³⁴⁰ <http://www.ncbi.nlm.nih.gov/pubmed/19004564> (2009)

³⁴¹ <http://www.ncbi.nlm.nih.gov/pubmed/22425036> (2012)

³⁴² <http://www.ncbi.nlm.nih.gov/pubmed/22235058> (2012)

³⁴³ <http://www.ncbi.nlm.nih.gov/pubmed/21893052> (2011)

³⁴⁴ <http://www.ncbi.nlm.nih.gov/pubmed/12643979> (2003)

³⁴⁵ <http://www.ncbi.nlm.nih.gov/pubmed/22656325> (2012)

³⁴⁶ <http://www.ncbi.nlm.nih.gov/pubmed/8249476> (1993)

³⁴⁷ <http://www.ncbi.nlm.nih.gov/pubmed/21535864> (2011)

8.29.2 Calcium

- Lower with FM³⁴⁸
- Higher with FM³⁴⁹
- Higher levels of calcium ions with FM^{350 351 352}

8.29.3 Copper

- Lower with FM³⁵³
- No difference with CFS³⁵⁴

8.29.4 Iron

- 69% of CFS patients are insufficient or deficient^{355 356}.
- Lower with FM^{357 358}
- Associated with restless legs syndrome³⁵⁹

8.29.5 Magnesium

- Lower in CFS, supplementation reduces symptoms^{360 361 362 363 364 365}
- Low in 45³⁶⁶ - 50%³⁶⁷ of CFS
- Lower with FM³⁶⁸
- Higher with FM³⁶⁹

8.29.6 Manganese

- Lower with FM³⁷⁰

³⁴⁸ <http://www.ncbi.nlm.nih.gov/pubmed/22022174> (2011)

³⁴⁹ <http://www.ncbi.nlm.nih.gov/pubmed/10626702> (1999)

³⁵⁰ <http://www.ncbi.nlm.nih.gov/pubmed/7968720> (1994)

³⁵¹ <http://www.ncbi.nlm.nih.gov/pubmed/11155461> (2000)

³⁵² <http://www.ncbi.nlm.nih.gov/pubmed/7968720> (1994)

³⁵³ <http://www.ncbi.nlm.nih.gov/pubmed/22022174> (2011)

³⁵⁴ <http://www.ncbi.nlm.nih.gov/pubmed/11470334> (2001)

³⁵⁵ <http://www.ncbi.nlm.nih.gov/pubmed/21886073> (2011)

³⁵⁶ <http://www.ncbi.nlm.nih.gov/pubmed/11470334> (2001)

³⁵⁷ <http://www.ncbi.nlm.nih.gov/pubmed/22022174> (2011)

³⁵⁸ <http://www.ncbi.nlm.nih.gov/pubmed/20087382> (2010)

³⁵⁹ <http://www.ncbi.nlm.nih.gov/pubmed/22727926> (2012)

³⁶⁰ <http://www.ncbi.nlm.nih.gov/pubmed/1672392> (1991)

³⁶¹ <http://www.ncbi.nlm.nih.gov/pubmed/21982120> (2011)

³⁶² <http://www.ncbi.nlm.nih.gov/pubmed/10872900> (2000)

³⁶³ <http://www.ncbi.nlm.nih.gov/pubmed/1492795> (1992)

³⁶⁴ <http://www.ncbi.nlm.nih.gov/pubmed/1672392> (1991)

³⁶⁵ <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2907931/?tool=pubmed> (2008)

³⁶⁶ <http://www.ncbi.nlm.nih.gov/pubmed/9513929> (1997)

³⁶⁷ <http://www.ncbi.nlm.nih.gov/pubmed/10872900> (2000)

³⁶⁸ <http://www.ncbi.nlm.nih.gov/pubmed/22022174> (2011)

³⁶⁹ <http://www.ncbi.nlm.nih.gov/pubmed/10626702> (1999)

³⁷⁰ <http://www.ncbi.nlm.nih.gov/pubmed/22022174> (2011)

8.29.7 Zinc

- Lower in CFS patients^{371 372}
- Associated with low Omega-3 levels
- Glutamine, N-acetyl cysteine and zinc in combination improves symptoms³⁷³

Milk fats

A recent New Scientist article³⁷⁴ found that milk fats caused a bacteria *Bilophila wadsworthia*, to go from zero to 6 per cent of the species found in the gut. This bacterium trigger inflammation by irritating the gut lining (making it more porous).

9 Brain Scans

There are several ways that CFS patients have had their brain scanned with modern technology. The three main methods are:

- Magnetic Resonance Imaging (MRI)
- Positron Emission Tomography (PET)
- Single-photon emission computerized tomography (SPECT)

SPECT scans has been the most consistent³⁷⁵.

9.1 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) studies are hit-and-miss for showing abnormalities^{376 377 378}.

Approximately 27%³⁷⁹ - 32%³⁸⁰ shows abnormal scans. Studies of Jarisch-Herxheimers Reactions (JHR) found that MRI's are affected by this reaction^{381 382}; this implies as symptoms waxes and wanes -- MRIs

³⁷¹ <http://www.ncbi.nlm.nih.gov/pubmed/16380690> (2005)

³⁷² <http://www.ncbi.nlm.nih.gov/pubmed/16338007> (2006)

³⁷³ <http://www.ncbi.nlm.nih.gov/pubmed/19112401> (2008)

³⁷⁴ <http://www.newscientist.com/article/dn21920-milk-fats-clue-to-inflammatory-bowel-disease.html>

³⁷⁵ <http://www.ncbi.nlm.nih.gov/pubmed/9134372> (1997)

³⁷⁶ <http://www.ncbi.nlm.nih.gov/pubmed/20223910> (2010)

³⁷⁷ <http://www.ncbi.nlm.nih.gov/pubmed/9282853> (1997)

³⁷⁸ <http://www.ncbi.nlm.nih.gov/pubmed/10761837> (2000)

³⁷⁹ <http://www.ncbi.nlm.nih.gov/pubmed/8138812> (1993)

³⁸⁰ <http://www.ncbi.nlm.nih.gov/pubmed/9282853> (1997)

³⁸¹ <http://www.ncbi.nlm.nih.gov/pubmed/21042805> (2011)

³⁸² <http://www.ncbi.nlm.nih.gov/pubmed/18302644> (2008)

may change. Similarly, if fatiguing tasks are occurring, MRI results may change. 35% of abnormal scans (10% of CFS scanned) suggested other known medical causes³⁸³. CFS subjects with MRI brain abnormalities report being more physically impaired than those patients without brain abnormalities³⁸⁴. MRIs is useful for excluding other possible causes for the fatigue.

MRI studies that found different issues (i.e. lack of consistency).

- Decrease white matter volume with level of fatigue³⁸⁵
- Decrease in gray matter volume³⁸⁶.
- No abnormal patterns in rate and extent of brain atrophy, ventricle volume, white matter lesions, cerebral blood flow or aqueductal CSF flow³⁸⁷.
- MR abnormalities consisted of foci of T2-bright signal in the periventricular and subcortical white matter and in the centrum semiovale³⁸⁸.
- Increased activation in the occipito-parietal cortex, posterior cingulate gyrus and parahippocampal gyrus, and decreased activation in dorsolateral and dorsomedial prefrontal cortex³⁸⁹
- Greater activity in several cortical and subcortical regions during the fatiguing cognitive task³⁹⁰.
- Significant differences in brain activation between the two groups as the demands of the task increased³⁹¹.
- Exerts greater effort to process auditory information³⁹².
- 78% of EBV-associated CFS patients³⁹³

9.2 Positron emission tomography

Positron emission tomography (PET)

- 50% shows abnormal scans³⁹⁴
- Significant hypometabolism in right mediofrontal cortex and brainstem³⁹⁵
- Hypometabolism bilaterally in the cingulate gyrus and the adjacent mesial cortical areas, decreased metabolism in the orbitofrontal cortex³⁹⁶.

³⁸³ <http://www.ncbi.nlm.nih.gov/pubmed/8138812> (1993)

³⁸⁴ <http://www.ncbi.nlm.nih.gov/pubmed/11328679> (2001)

³⁸⁵ <http://www.ncbi.nlm.nih.gov/pubmed/21560176> (2011)

³⁸⁶ <http://www.ncbi.nlm.nih.gov/pubmed/15955487> (2005)

³⁸⁷ <http://www.ncbi.nlm.nih.gov/pubmed/20223910> (2010)

³⁸⁸ <http://www.ncbi.nlm.nih.gov/pubmed/8141020> (1994 *)

³⁸⁹ <http://www.ncbi.nlm.nih.gov/pubmed/18447963> (2008)

³⁹⁰ <http://www.ncbi.nlm.nih.gov/pubmed/17408973> (2007)

³⁹¹ <http://www.ncbi.nlm.nih.gov/pubmed/17079703> (2006)

³⁹² <http://www.ncbi.nlm.nih.gov/pubmed/15907308> (2005)

³⁹³ <http://www.ncbi.nlm.nih.gov/pubmed/1309285> (1992)

³⁹⁴ <http://www.ncbi.nlm.nih.gov/pubmed/12810781> (2003 *)

³⁹⁵ <http://www.ncbi.nlm.nih.gov/pubmed/9790483> (1998)

³⁹⁶ <http://www.ncbi.nlm.nih.gov/pubmed/12810781> (2003)

- Decreased 5-HT1A receptor number affinity³⁹⁷

9.3 Transcranial Doppler Sonography

- Cerebral blood flow is less effective with POTS³⁹⁸ (slower response).
- Less cerebral blood flow than controls³⁹⁹
- Shorter time to orthostatic symptoms⁴⁰⁰.

9.4 SPECT

Single-photon emission computerized tomography (SPECT) scans are the most reliable for CFS.

- 80%⁴⁰¹ - 81%⁴⁰² shows abnormal scans
- SPECT abnormalities appeared to correlate with clinical status⁴⁰³
- Defects were located predominantly in the frontal and temporal lobes. Midcerebral uptake index was found to be significantly lower⁴⁰⁴
- Lower cortical/cerebellar rCBF ratios⁴⁰⁵
 - In monozygotic twins (one with CFS, one without CFS), the same patterns were seen⁴⁰⁶
- 80% had lower global cerebral blood flow⁴⁰⁷
- Diffuse regional cerebral blood flow⁴⁰⁸
- Abnormal cerebral perfusion patterns^{409 410}
- Reduced absolute cortical blood flow in rather broad areas⁴¹¹
- Reduced cortical blood flow in the distribution of both right and left middle cerebral arteries⁴¹²
- Blood flow in the left basal ganglia and thalamus was markedly higher⁴¹³
- Serum TGF-beta and cerebral blood flow abnormalities accentuated after exercise⁴¹⁴

10 Symptoms

In addition to the usual symptoms, the following has been reported with incidence percentage^{415 416}

-
- ³⁹⁷ <http://www.ncbi.nlm.nih.gov/pubmed/15691524> (2005)
 - ³⁹⁸ <http://www.ncbi.nlm.nih.gov/pubmed/19502561> (2009 *)
 - ³⁹⁹ <http://www.ncbi.nlm.nih.gov/pubmed/22180650> (2012)
 - ⁴⁰⁰ <http://www.ncbi.nlm.nih.gov/pubmed/12593133> (2003)
 - ⁴⁰¹ <http://www.ncbi.nlm.nih.gov/pubmed/1491843> (1992)
 - ⁴⁰² <http://www.ncbi.nlm.nih.gov/pubmed/8141020> (1994 *)
 - ⁴⁰³ <http://www.ncbi.nlm.nih.gov/pubmed/8141020> (1994 *)
 - ⁴⁰⁴ <http://www.ncbi.nlm.nih.gov/pubmed/8141022> (1994 *)
 - ⁴⁰⁵ <http://www.ncbi.nlm.nih.gov/pubmed/1491843> (1992)
 - ⁴⁰⁶ <http://www.ncbi.nlm.nih.gov/pubmed/11376266> (2001)
 - ⁴⁰⁷ <http://www.ncbi.nlm.nih.gov/pubmed/21167506> (2011)
 - ⁴⁰⁸ <http://www.ncbi.nlm.nih.gov/pubmed/12554824> (2003)
 - ⁴⁰⁹ <http://www.ncbi.nlm.nih.gov/pubmed/10974961> (2000 *)
 - ⁴¹⁰ <http://www.ncbi.nlm.nih.gov/pubmed/8542261> (1995)
 - ⁴¹¹ <http://www.ncbi.nlm.nih.gov/pubmed/16494597> (2006)
 - ⁴¹² <http://www.ncbi.nlm.nih.gov/pubmed/16494597> (2006)
 - ⁴¹³ <http://www.ncbi.nlm.nih.gov/pubmed/10761837> (2000)
 - ⁴¹⁴ <http://www.ncbi.nlm.nih.gov/pubmed/7496949> (1994)

- Shortness of breath (32%)
- Dyspnea on effort (28%),
- Rapid heartbeat or tachycardia (18% - 38%),
- Chest pain (43%),
- Neurally-mediated syncope (21%)
- Fainting (43%),
- Orthostatic dizziness (40% - 45%)
- Coldness of feet (42%), were all frequent complaints.
- Hypotension (28%) was occasionally noted.
- Electrocardiograms with right axis deviation (21%) and
- Severe sinus arrhythmia (34%)
- Small heart shadow (cardiothoracic ratio $\leq 42\%$) patients (60%)
- Low heart stroke volume (36%)

11 Supplements

I classify supplements into 4 groups:

- Positive effects (take)
- Negative effects (don't take)
- No information (likely safe)
- Mixed effects (avoid if practical -- substitute alternatives)

Using an in vitro thrombolytic model, *Tinospora cordifolia*, *Rubia cordifolia*, *Hemidesmus indicus*, *Glycyrrhiza glabra* Linn, *Fagonia Arabica* and *Bacopa monnieri* Linn showed 19.3%, 14.5%, 20.3%, 17.8%, 75.6% and 41.8% clot lysis respectively. Among the herbs studied *Fagonia arabica* showed significant % of clot lysis (75.6%) with reference to Streptokinase (86.2%).⁴¹⁷

11.1.1 Aloe

Reduces IL-1 β and TNF- α ⁴¹⁸

11.1.2 Alpha Lipoic Acid

- Lowers CD62P platelet expression⁴¹⁹
- Reduces CRP levels by 19%⁴²⁰
- Decreases symptoms of neuropathy and neuropathic deficit⁴²¹.
- Decreases fibrinogen, factor VII, vWF, and triglycerides⁴²²

⁴¹⁵ <http://www.ncbi.nlm.nih.gov/pubmed/19881233> (2009 *)

⁴¹⁶ <http://www.ncbi.nlm.nih.gov/pubmed/10189122> (1999)

⁴¹⁷ <http://www.ncbi.nlm.nih.gov/pubmed/17986325> (2007)

⁴¹⁸ <http://www.ncbi.nlm.nih.gov/pubmed/21277867> (2011)

⁴¹⁹ <http://www.ncbi.nlm.nih.gov/pubmed/22228743> (2012)

⁴²⁰ <http://www.ncbi.nlm.nih.gov/pubmed/21908204> (2012)

⁴²¹ <http://www.ncbi.nlm.nih.gov/pubmed/20519180> (2010)

⁴²² <http://www.ncbi.nlm.nih.gov/pubmed/11474472> (2001)

- Decreases tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6)⁴²³
- Improves blood flow and nerve function⁴²⁴.
- Reduces plasma levels of free fatty acids (FFAs), triglyceride (TG), total cholesterol (T-Chol), low density lipoprotein-cholesterol (LDL-Chol), small dense LDL-Chol (sd-LDL), oxidized LDL-Chol (ox-LDL-Chol), very low density lipoprotein-cholesterol (VLDL-Chol)⁴²⁵

11.1.3 Antidepressants

- No better than placebo⁴²⁶

11.1.4 Beta Glucan

- Beta Glucan

11.1.5 B-Vitamins

11.1.5.1 Folate

11.1.5.2 B12

Deficiency increases TNF-alpha⁴²⁷

11.1.5.3 B12 + Folate

- Reduces TNF-alpha and IL-6⁴²⁸

11.1.6 Boswellia Gum

Gum-resin extracts of *Boswellia serrata* have been traditionally used in folk medicine for centuries to treat various chronic inflammatory diseases⁴²⁹. It has been found to have antibacterial⁴³⁰, anti-arthritic⁴³¹, anti-edematous⁴³², antioxidant, antiplatelet and anticoagulant (equivalent to heparin)⁴³³. positive effects of BEs in some chronic inflammatory diseases including rheumatoid arthritis, bronchial asthma, osteoarthritis, ulcerative colitis and Crohn's disease have been reported⁴³⁴.

- Inhibited clotting factors Xa and Xia
- Inhibited ADP induced platelet aggregation
- Major increase of coagulation time
- Major increase of prothrombin time

⁴²³ <http://www.ncbi.nlm.nih.gov/pubmed/21593803> (2011)

⁴²⁴ <http://www.ncbi.nlm.nih.gov/pubmed/11474472> (2001)

⁴²⁵ <http://www.ncbi.nlm.nih.gov/pubmed/21593803> (2011)

⁴²⁶ <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2907931/> (2008)

⁴²⁷ <http://www.ncbi.nlm.nih.gov/pubmed/11722601> (2001)

⁴²⁸ <http://www.ncbi.nlm.nih.gov/pubmed/16214333> (2006)

⁴²⁹ <http://www.ncbi.nlm.nih.gov/pubmed/22457547> (2011)

⁴³⁰ <http://www.ncbi.nlm.nih.gov/pubmed/22422529> (2012)

⁴³¹ <http://www.ncbi.nlm.nih.gov/pubmed/21479939> (2011)

⁴³² <http://www.ncbi.nlm.nih.gov/pubmed/21855244> (2011)

⁴³³ <http://www.ncbi.nlm.nih.gov/pubmed/21771654> (2011)

⁴³⁴ <http://www.ncbi.nlm.nih.gov/pubmed/20696559> (2010)

- Major increase of activated partial thromboplastin time
- Decrease of TNF-alpha, IL-1, IL-2, IL-4, IL-6 and IFN-gamma⁴³⁵,
- Reduces CPR levels⁴³⁶

11.1.7 Bromelain

Bromelain shown conflicting effects on the release of various cytokines⁴³⁷. Studies reports that it increases⁴³⁸ or reduces⁴³⁹ factor-alpha (TNF-alpha), interleukin-1-beta (IL-1 beta), and interleukin-6 (IL-6) antifungal⁴⁴⁰, anti-edema, antiinflammatory, and coagulation-inhibiting effects⁴⁴¹

- Has anti-edema, antiinflammatory, and coagulation-inhibiting effects⁴⁴²
- Increases serum fibrinolytic activity, reduces fibrinogen synthesis, and directly degrades fibrin and fibrinogen⁴⁴³.
- Increased penetration of antibiotics^{444 445 446 447 448}
- Reduces CD14, TNF-alpha, COX-2
- Degrades TNF-alpha and IL-1beta molecules⁴⁴⁹
- Impact plateaus at 12-16 hours⁴⁵⁰
- tetracyclines^{451 452 453}
- enhancement of the serum fibrinolytic activity,
- inhibition of the fibrinogen synthesis,
- direct degradation of fibrin and fibrinogen⁴⁵⁴
- acts as fibrinolysis enzyme activator⁴⁵⁵

11.1.8 Coenzyme Q10

- ~ 45% of CFS patients have low levels⁴⁵⁶
- Supplementation helped ~70%⁴⁵⁷, reduced headaches⁴⁵⁸

⁴³⁵ <http://www.ncbi.nlm.nih.gov/pubmed/20696559> (2010)

⁴³⁶ <http://www.ncbi.nlm.nih.gov/pubmed/22017619> (2012)

⁴³⁷ <http://www.ncbi.nlm.nih.gov/pubmed/22517542> (2012)

⁴³⁸ <http://www.ncbi.nlm.nih.gov/pubmed/7529614> (1994)

⁴³⁹ <http://www.ncbi.nlm.nih.gov/pubmed/18569070> (2008)

⁴⁴⁰ <http://www.ncbi.nlm.nih.gov/pubmed/22537505> (2012)

⁴⁴¹ <http://www.ncbi.nlm.nih.gov/pubmed/2203073> (1990)

⁴⁴² <http://www.ncbi.nlm.nih.gov/pubmed/2203073> (1990)

⁴⁴³ <http://www.ncbi.nlm.nih.gov/pubmed/2203073> (1990)

⁴⁴⁴ <http://www.ncbi.nlm.nih.gov/pubmed/3467190> (1986)

⁴⁴⁵ <http://www.ncbi.nlm.nih.gov/pubmed/397422> (1978)

⁴⁴⁶ <http://www.ncbi.nlm.nih.gov/pubmed/4542541> (1973)

⁴⁴⁷ <http://www.ncbi.nlm.nih.gov/pubmed/4623701> (1972)

⁴⁴⁸ <http://www.ncbi.nlm.nih.gov/pubmed/5603008> (1967)

⁴⁴⁹ <http://www.ncbi.nlm.nih.gov/pubmed/18569070> (2008)

⁴⁵⁰ <http://www.ncbi.nlm.nih.gov/pubmed/7529614> (1994)

⁴⁵¹ <http://www.ncbi.nlm.nih.gov/pubmed/4623701> (1972)

⁴⁵² <http://www.ncbi.nlm.nih.gov/pubmed/728330> (1978)

⁴⁵³ <http://www.ncbi.nlm.nih.gov/pubmed/3467190> (1986)

⁴⁵⁴ <http://www.ncbi.nlm.nih.gov/pubmed/2203073> (1990)

⁴⁵⁵ <http://www.ncbi.nlm.nih.gov/pubmed/7199897> (1981)

⁴⁵⁶ <http://www.ncbi.nlm.nih.gov/pubmed/20010505> (2009)

- Low levels are associated with worst headaches⁴⁵⁹
- Reduces blood clotting⁴⁶⁰
- Improves mitochondrial function⁴⁶¹

11.1.8.1 Ubiquinol

- Ubiquinol (a version of CoQ10) had no CFS studies⁴⁶²

11.1.8.2 Ibedenone

CoQ 10 Analogue

- Improves mitochondrial function⁴⁶³
- Improves neurological function^{464 465 466}

11.1.9 Dehydroepiandrosterone (DHEA)

Dehydroepiandrosterone (DHEA) is a steroid hormone secreted primarily by the adrenal glands. It is the most abundant circulating steroid in humans with a key role in a wide range of physiological responses. Circulating levels of DHEA decline with age and a relationship has been suggested between lower DHEA levels and heart disease, cancer, diabetes, obesity, chronic fatigue syndrome, AIDS, and Alzheimer's disease⁴⁶⁷.

- Supplementation helped 65%^{468 469}
 - pain improved: 18%
 - fatigue decreased: 21%,
 - daily living improved: 8.5
 - helplessness decreased: 11%,
 - anxiety decreased: 35%,
 - thinking improved: 26%,
 - memory improved: 17%
 - sexual problems improved: 22%
- No effect but belief that it may help is significant factor in comorbid syndrome⁴⁷⁰
- No effect on patients with adrenal insufficiency⁴⁷¹.

⁴⁵⁷ <http://www.ncbi.nlm.nih.gov/pubmed/15889950> (2005)

⁴⁵⁸ <http://www.ncbi.nlm.nih.gov/pubmed/22532869> (2012)

⁴⁵⁹ <http://www.ncbi.nlm.nih.gov/pubmed/22532869> (2012)

⁴⁶⁰ <http://www.ncbi.nlm.nih.gov/pubmed/20617421> (2010)

⁴⁶¹ <http://www.ncbi.nlm.nih.gov/pubmed/16205466> (2005)

⁴⁶² As of July, 4, 2012, PubMed had no citations

⁴⁶³ <http://www.ncbi.nlm.nih.gov/pubmed/22086148> (2012)

⁴⁶⁴ <http://www.ncbi.nlm.nih.gov/pubmed/21779958> (2012)

⁴⁶⁵ <http://www.ncbi.nlm.nih.gov/pubmed/19430983> (2009)

⁴⁶⁶ <http://www.ncbi.nlm.nih.gov/pubmed/7988944> (1994)

⁴⁶⁷ <http://www.ncbi.nlm.nih.gov/pubmed/11410076> (2001)

⁴⁶⁸ <http://www.ncbi.nlm.nih.gov/pubmed/15889950> (2005)

⁴⁶⁹ <http://www.ncbi.nlm.nih.gov/pubmed/19078357> (1999)

⁴⁷⁰ <http://www.ncbi.nlm.nih.gov/pubmed/17545193> (2008)

⁴⁷¹ <http://www.ncbi.nlm.nih.gov/pubmed/19773400> (2009)

- Lower levels found in CFS patients^{472 473 474 475}
- Higher levels found in CFS patients with higher level more fatigued⁴⁷⁶
- Lower level correlate with fatigue in other illnesses⁴⁷⁷.
- No significant difference found^{478 479 480}.
- CFS patients respond different to DHEA stimulation⁴⁸¹ (a blunted serum DHEA response curve)⁴⁸².

11.1.10 EDTA

Ethylenediaminetetraacetic acid (EDTA) is a chelating agent for iron, mercury, lead and aluminum.

- Effective for reducing levels with improvement of symptoms for other autoimmune illnesses^{483 484}.
- Effective for treating vascular disease⁴⁸⁵
- Taken with citric acid may improve effect⁴⁸⁶
- Inhibits biofilm^{487 488 489 490} (a mechanism used by some pathogens to persist)
 - Biofilms are seen with Lyme and various tick borne infections⁴⁹¹

11.1.11 Evening Primrose Oil

- Increases in fibrinogen, factor VII, vWF, triglycerides, and cholesterol and a significant decrease in high-density lipoprotein⁴⁹².
- Improves blood flow⁴⁹³.
- Decreased platelet count⁴⁹⁴.

⁴⁷² <http://www.ncbi.nlm.nih.gov/pubmed/16264414> (2005)

⁴⁷³ <http://www.ncbi.nlm.nih.gov/pubmed/11470334> (2001)

⁴⁷⁴ <http://www.ncbi.nlm.nih.gov/pubmed/10403156> (1999)

⁴⁷⁵ <http://www.ncbi.nlm.nih.gov/pubmed/9852212> (1998)

⁴⁷⁶ <http://www.ncbi.nlm.nih.gov/pubmed/15110921> (2004)

⁴⁷⁷ <http://www.ncbi.nlm.nih.gov/pubmed/17669554> (2008)

⁴⁷⁸ <http://www.ncbi.nlm.nih.gov/pubmed/15730417> (2005)

⁴⁷⁹ <http://www.ncbi.nlm.nih.gov/pubmed/15058215> (2003)

⁴⁸⁰ <http://www.ncbi.nlm.nih.gov/pubmed/12700181> (2003)

⁴⁸¹ <http://www.ncbi.nlm.nih.gov/pubmed/11104854> (2000)

⁴⁸² <http://www.ncbi.nlm.nih.gov/pubmed/10077344> (1999)

⁴⁸³ <http://www.ncbi.nlm.nih.gov/pubmed/22438029> (2012)

⁴⁸⁴ <http://www.ncbi.nlm.nih.gov/pubmed/21655943> (2011)

⁴⁸⁵ <http://www.ncbi.nlm.nih.gov/pubmed/8820322> (1996)

⁴⁸⁶ <http://www.ncbi.nlm.nih.gov/pubmed/12643979> (2003)

⁴⁸⁷ <http://www.ncbi.nlm.nih.gov/pubmed/22029913> (2012)

⁴⁸⁸ <http://www.ncbi.nlm.nih.gov/pubmed/17909983> (2007)

⁴⁸⁹ <http://www.ncbi.nlm.nih.gov/pubmed/18594291> (2008)

⁴⁹⁰ <http://www.ncbi.nlm.nih.gov/pubmed/21864314> (2012)

⁴⁹¹ <http://www.ncbi.nlm.nih.gov/pubmed/21694904> (2011)

⁴⁹² <http://www.ncbi.nlm.nih.gov/pubmed/11474472> (2001)

⁴⁹³ <http://www.ncbi.nlm.nih.gov/pubmed/11474472> (2001)

⁴⁹⁴ <http://www.ncbi.nlm.nih.gov/pubmed/19783511> (2009)

- Effective in some CFS patients⁴⁹⁵.
- No significant difference in a long term study⁴⁹⁶

IMHO: Avoid, use Alpha Lipoic Acid instead.

11.1.12 Galantamine

- No better than placebo⁴⁹⁷.

11.1.13 Ginger

- Reduces CPR levels⁴⁹⁸

11.1.14 Ginseng

- Supplementation helped 56%⁴⁹⁹

11.1.15 Ginkgo biloba

- Reduces IL-6⁵⁰⁰
- Increase IL-4⁵⁰¹
- No impact on IL-1 β and TNF- α ⁵⁰²
- Reduces the anticoagulant action of warfarin.⁵⁰³
- Questionable if any impact on coagulation⁵⁰⁴

11.1.16 Grape Seed Extract

Grape seed extract is rich in proanthocyanidins. Proanthocyanidins are available from other supplements (cranberry juice, cider). There are contradictory reports on whether it increases^{505 506} or decreases^{507 508 509} IL6, IL8, TNF-alpha. It may or may not offer protection for glutamate excitotoxicity (depends on grapes being used)⁵¹⁰.

- decrease in uPA and PAI-1 activities and thus decreased fibrinolytic activity⁵¹¹
- inhibitory effect on platelets^{512 513}

⁴⁹⁵ <http://www.ncbi.nlm.nih.gov/pubmed/8616424> (1996)

⁴⁹⁶ http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2907931/?tool=pubmed#BMJ_1101_18 (2008)

⁴⁹⁷ <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2907931/?tool=pubmed> (2008)

⁴⁹⁸ <http://www.ncbi.nlm.nih.gov/pubmed/22017619> (2012)

⁴⁹⁹ <http://www.ncbi.nlm.nih.gov/pubmed/15889950> (2005)

⁵⁰⁰ <http://www.ncbi.nlm.nih.gov/pubmed/22553973> (2012)

⁵⁰¹ <http://www.ncbi.nlm.nih.gov/pubmed/20388480> (2010)

⁵⁰² <http://www.ncbi.nlm.nih.gov/pubmed/22345884> (2012)

⁵⁰³ <http://www.ncbi.nlm.nih.gov/pubmed/21802929> (2012)

⁵⁰⁴ <http://www.ncbi.nlm.nih.gov/pubmed/15166915> (2004)

⁵⁰⁵ <http://www.ncbi.nlm.nih.gov/pubmed/21995732> (2011)

⁵⁰⁶ <http://www.ncbi.nlm.nih.gov/pubmed/21484436> (2011)

⁵⁰⁷ <http://www.ncbi.nlm.nih.gov/pubmed/21095090> (2011)

⁵⁰⁸ <http://www.ncbi.nlm.nih.gov/pubmed/19560935> (2009)

⁵⁰⁹ <http://www.ncbi.nlm.nih.gov/pubmed/18602813> (2009)

⁵¹⁰ <http://www.ncbi.nlm.nih.gov/pubmed/21283677> (2011)

⁵¹¹ <http://www.ncbi.nlm.nih.gov/pubmed/19640694> (2010)

⁵¹² <http://www.ncbi.nlm.nih.gov/pubmed/15567462> (2005)

- With L-arginine reduces fatigue⁵¹⁴
- Reduces fatigue⁵¹⁵
- Increases antithrombin activity⁵¹⁶
- Reduces IL-1 β , TNF- α , IL-6 and IL-8^{517 518}
- Increases TNF- α ⁵¹⁹
- Reduces COX2⁵²⁰
- Reduces IL-17, IL-6⁵²¹
- Decreased fibrinolytic activity, Decreased cell-surface plasmin activity.^{522 523}
- Reduces thrombus formation, inhibitory effect on platelets⁵²⁴.

11.1.17 Glutamate

Monosodium glutamate (MSG) is often added to food to improve favor.

- Significant return of symptoms in FM⁵²⁵.
- Decreased quality of life in regards to IBS symptoms⁵²⁶
- Worsening of fibromyalgia severity⁵²⁷

11.1.18 L-Arginine

- Does not increase NK activity in CFS patients, does in Controls⁵²⁸
- Low levels⁵²⁹

11.1.19 L-Carnitine

Also known as acetyl l-carnitine mainly utilized for the biosynthesis of glutamate⁵³⁰.

- Levels of biosynthesis of neurotransmitters through acetylcarnitine might be reduced in some brain regions of chronic fatigue patients⁵³¹
- Acety l-carnitine improves mental fatigue and propiony l-carnitine improves general fatigue⁵³².

⁵¹³ <http://www.ncbi.nlm.nih.gov/pubmed/16160595> (2005)

⁵¹⁴ <http://www.ncbi.nlm.nih.gov/pubmed/20386475> (2010)

⁵¹⁵ <http://www.ncbi.nlm.nih.gov/pubmed/15630197> (2004)

⁵¹⁶ <http://www.ncbi.nlm.nih.gov/pubmed/20726345> (2010)

⁵¹⁷ <http://www.ncbi.nlm.nih.gov/pubmed/22563853> (2012)

⁵¹⁸ <http://www.ncbi.nlm.nih.gov/pubmed/21484436> (2011)

⁵¹⁹ <http://www.ncbi.nlm.nih.gov/pubmed/21995732> (2011)

⁵²⁰ <http://www.ncbi.nlm.nih.gov/pubmed/20143255> (2010)

⁵²¹ <http://www.ncbi.nlm.nih.gov/pubmed/21484436> (2011)

⁵²² <http://www.ncbi.nlm.nih.gov/pubmed/19640694> (2010)

⁵²³ <http://www.ncbi.nlm.nih.gov/pubmed/3161536> (1985)

⁵²⁴ <http://www.ncbi.nlm.nih.gov/pubmed/15567462> (2005)

⁵²⁵ <http://www.ncbi.nlm.nih.gov/pubmed/22766026> (2012)

⁵²⁶ <http://www.ncbi.nlm.nih.gov/pubmed/22766026> (2012)

⁵²⁷ <http://www.ncbi.nlm.nih.gov/pubmed/22766026> (2012)

⁵²⁸ <http://www.ncbi.nlm.nih.gov/pubmed/9824439> (1998)

⁵²⁹ <http://www.ncbi.nlm.nih.gov/pubmed/8475696> (1993)

⁵³⁰ <http://www.ncbi.nlm.nih.gov/pubmed/12414265> (2002)

⁵³¹ <http://www.ncbi.nlm.nih.gov/pubmed/12414265> (2002)

- Reduces IL-6 but no impact on TNF-alpha, IL-1beta⁵³³
- Improves pain levels in FM⁵³⁴ (500 mg x 3 times/day)
- Reduced by Azithromycin⁵³⁵

11.1.20 Licorice

Spezzata (pure Licorice - Glycyrrhia).

- Reduces (TNF- α), interleukin (IL)-6⁵³⁶, and IL-1 β ⁵³⁷ and IL-8⁵³⁸
- Increases plasma recalcification, thrombin and fibrinogen clotting times⁵³⁹,
- Reduces thrombin-induced, but not collagen-, PAF- or convulxin-induced platelet aggregation.⁵⁴⁰
- Improves CFS symptoms⁵⁴¹
- Potentiate the action of hydrocortisone⁵⁴².
- Prolong the biological half-life of cortisol⁵⁴³

11.1.21 Lumbrokinase

- antithrombotic⁵⁴⁴
- digested fibrinogen and inhibited platelet adhesion⁵⁴⁵
- fibrinogen decreased significantly. Inhibition of intrinsic coagulation pathway and the activation of fibrinolysis via an increase of t-PA activity⁵⁴⁶
- Maximum dosage: 60 mg/day⁵⁴⁷

11.1.22 Mastic Gum

This gum was mentioned by ancient Greek Physicians (Herodotus, Dioscorides and Galen) and in most of the older medical works. It has been found to have antimicrobial⁵⁴⁸, antifungal, antioxidant, hypolipidemic, anti-inflammatory, anti-Crohn and anticancer activities. In mice studies, a 100% inhibition of inflammation⁵⁴⁹ has been observed.

⁵³² <http://www.ncbi.nlm.nih.gov/pubmed/15039515> (2004)

⁵³³ <http://www.ncbi.nlm.nih.gov/pubmed/20812958> (2010)

⁵³⁴ <http://www.ncbi.nlm.nih.gov/pubmed/17543140> (2007)

⁵³⁵ <http://www.translational-medicine.com/content/4/1/34/>

⁵³⁶ <http://www.ncbi.nlm.nih.gov/pubmed/22422925> (2012)

⁵³⁷ <http://www.ncbi.nlm.nih.gov/pubmed/21644799> (2011)

⁵³⁸ <http://www.ncbi.nlm.nih.gov/pubmed/18771378> (2008)

⁵³⁹ <http://www.ncbi.nlm.nih.gov/pubmed/9196073> (1997)

⁵⁴⁰ <http://www.ncbi.nlm.nih.gov/pubmed/9196073> (1997)

⁵⁴¹ <http://archinte.jamanetwork.com/article.aspx?articleid=210216>

⁵⁴² <http://www.ncbi.nlm.nih.gov/pubmed/1970371> (1990)

⁵⁴³ <http://www.ncbi.nlm.nih.gov/pubmed/2384181> (1990)

⁵⁴⁴ <http://www.ncbi.nlm.nih.gov/pubmed/12483186> (2002)

⁵⁴⁵ <http://www.ncbi.nlm.nih.gov/pubmed/1960890> (1991)

⁵⁴⁶ <http://www.ncbi.nlm.nih.gov/pubmed/11321442> (2000)

⁵⁴⁷ <http://www.researchednutritionals.com/store/item.cfm?code=CBD202>

⁵⁴⁸ <http://www.ncbi.nlm.nih.gov/pubmed/19414406> (2009 *)

⁵⁴⁹ <http://www.ncbi.nlm.nih.gov/pubmed/21061835> (2010)

- Effective against Helicobacter pylori^{550 551 552},
- Eliminates TNF-alpha overproduction⁵⁵³
- Reduces NO production⁵⁵⁴

11.1.23 Melatonin

- Lower levels at night^{555 556}
- No difference^{557 558}
- Higher at night in FM⁵⁵⁹
- 3mg helped in FM^{560 561 562}
- Ambiguous results⁵⁶³

11.1.24 Milk Thistle

http://www.hcvadvocate.org/news/NewsUpdates_pdf/2.4.3_HCV_Advocate_2001/advocate011.pdf

Researchers at the University of Pittsburgh have suspected that milk thistle can slow down or reduce the activity of enzymes in the liver. What does this have to do with HIV? you might ask. Well, enzymes in the liver break down many of the substances that we eat and drink, including medications. If the activity of these enzymes are reduced, then drugs remain in the blood longer than they otherwise might. This could lead to having higher-than-expected levels of drugs in the body, causing side effects or intensifying already-existing side effects.

Indeed, in recent experiments using milk thistle and human liver cells, the researchers found that relatively small concentrations of milk thistle did significantly slow down the activity of the liver enzyme CYP3A4 by 50% to 100%. Many medications taken by people with HIV/AIDS (PHAs) - such as protease inhibitors and non-nukes - are processed by this liver enzyme.

If milk thistle is taken by someone using protease inhibitors or non-nukes, it has the potential to raise levels of these drugs, causing unpleasant or even dangerous side effects.

Below is a short list of some other medications that are processed through the CYP3A4 enzyme. Levels of these medications may increase if taken by people who are also using milk thistle. This list is not exhaustive:

methadone

heart drugs – Tambacor (flecainide), Rythmol (propafenone)

antibiotics – erythromycin, rifampin

anti-seizure drugs – carbamazepine (Tegretol)

antidepressants – St. John's wort, Zyban/Wellbutrin (bupropion), Paxil (paroxetine), Prozac (fluoxetine), Luvox (fluvoxetine) Serzone (nefazodone), Zoloft (sertraline), Effexor (venlafaxine)

⁵⁵⁰ <http://www.ncbi.nlm.nih.gov/pubmed/22414110> (2012)

⁵⁵¹ <http://www.ncbi.nlm.nih.gov/pubmed/22346256> (2012)

⁵⁵² <http://www.ncbi.nlm.nih.gov/pubmed/19879118> (2010)

⁵⁵³ <http://www.ncbi.nlm.nih.gov/pubmed/21645369> (2011 *)

⁵⁵⁴ <http://www.ncbi.nlm.nih.gov/pubmed/19567394> (2009 *)

⁵⁵⁵ <http://www.ncbi.nlm.nih.gov/pubmed/21682138> (2011)

⁵⁵⁶ <http://www.ncbi.nlm.nih.gov/pubmed/9828904> (1998)

⁵⁵⁷ <http://www.ncbi.nlm.nih.gov/pubmed/22193230> (2011)

⁵⁵⁸ <http://www.ncbi.nlm.nih.gov/pubmed/9517780> (1998)

⁵⁵⁹ <http://www.ncbi.nlm.nih.gov/pubmed/10606381> (1999)

⁵⁶⁰ <http://www.ncbi.nlm.nih.gov/pubmed/10752492> (2000)

⁵⁶¹ <http://www.ncbi.nlm.nih.gov/pubmed/17894923> (2007)

⁵⁶² <http://www.ncbi.nlm.nih.gov/pubmed/21158908> (2011)

⁵⁶³ <http://www.ncbi.nlm.nih.gov/pubmed/20423309> (2010)

antihistamines – Hismanal (astemizole), Seldane (terfenadine)
antifungals – itraconazole (Sporanox), Ketoconazole (Nizoral)
gastrointestinal motility agents – Prepulsid (Cisapride)
ergot drugs – Ergonovine, Ergomar (ergotamine)
anti-psychotics – Clozaril (clozapine), Orap (pimozide)
sedatives/sleeping pills – Ambien (zolpidem), Halcion (triazolam), Versed (midazolam)
lipid-lowering drugs (statins) – Lescol (fluvastatin), Mevacor (lovastatin), Pravachol (pravastatin) and Zocor (simvastatin), Baycol (cerivastatin)
transplant drugs – cyclosporine (Neoral, Sandimmune), ProGraf (tacrolimus)

Milk thistle also has the potential to lower levels of the following drugs:

anti-parasite drugs – Mepron (atovaquone)
sedatives/sleeping pills – Ativan (lorazepam)
hormones – estrogen

I quickly searched 'milk thistle cautions' and also found 1 example of raised liver enzymes with it. (the mayo clinic)

I know we've had the CB12 conversation before, but if you're liver is unhappy..... :-)

Jacqui

11.1.25 [Monolaurin \(Glyceryl laurate\)](#)

11.1.26 [Myrrh Gum](#)

Myrrh is a complex gum⁵⁶⁴ with antimicrobial⁵⁶⁵, antifungal⁵⁶⁶, antiseptic, anesthetic, and antitumor properties⁵⁶⁷. It increased glucose tolerance⁵⁶⁸.

inhibited the production of NO, PGE(2), IL-1 β and TNF- α ⁵⁶⁹

11.1.27 [NAC](#)

N-Acetyl-Cysteine (NAC) or acetylcysteine is an amino acid used as thiol reducer to burst EB phase of Cpn, and supports liver as glutathione precursor⁵⁷⁰. It is also known as thiamphenicol glycinate acetylcysteinate⁵⁷¹

- Used by [ChPn⁵⁷²]

⁵⁶⁴ <http://www.ncbi.nlm.nih.gov/pubmed/16170385> (2005 *), <http://mefanet.upol.cz/BP/2005/1/3.pdf>

⁵⁶⁵ <http://www.ncbi.nlm.nih.gov/pubmed/12685809> (2003)

⁵⁶⁶ <http://www.ncbi.nlm.nih.gov/pubmed/22246961> (2012)

⁵⁶⁷ <http://www.ncbi.nlm.nih.gov/pubmed/17978635> (2007)

⁵⁶⁸ <http://www.ncbi.nlm.nih.gov/pubmed/3618079> (1987)

⁵⁶⁹ <http://www.ncbi.nlm.nih.gov/pubmed/21827494> (2011)

⁵⁷⁰ http://www.cpnhelp.org/chlamydia_pneumoniae/supp

⁵⁷¹ http://www.chemicalbook.com/ChemicalProductProperty_EN_CB7900217.htm

- User by [ChPH⁵⁷³] – Stratton Protocol. 600 mg/day
- Improves antibiotic effectiveness⁵⁷⁴
 - Treatment prior to starting antibiotic therapy eliminates biofilm^{575 576 577 578 579}
- Improves 59% of CFS patients after 10-14 months⁵⁸⁰

11.1.28 NADH

Nicotinamide adenine dinucleotide (NADH). This is precursor for niacin

- Supplementation helped^{581 582 583}
- Levels lower in CFS patients⁵⁸⁴
- Effect may last only 3 months⁵⁸⁵
- Helpful for 31% of CFS patients⁵⁸⁶
- Reported effects not confirmed in later studies⁵⁸⁷

11.1.29 Naltrexone

Naltrexone is an opioid receptor antagonist used primarily in the management of alcohol dependence and opioid dependence

- Naltrexone administration increased the production of IL-2, IL-4, and IL-6⁵⁸⁸
- Decreases interleukin (IL)-6 and IL-12⁵⁸⁹

11.1.30 Nattokinase

Nattokinase is from a fermented-soya desert food in Japan called Natto.

antihypertensive⁵⁹⁰

- decrease of red blood cell aggregation
- lower shear-viscosity of blood cells⁵⁹¹

⁵⁷² <http://chlamydia-pneumoniae.org/treatment.html>

⁵⁷³ http://www.cpnhelp.org/emerging_stratton_protocol

⁵⁷⁴ <http://www.ncbi.nlm.nih.gov/pubmed/11304944> (2001)

⁵⁷⁵ <http://www.ncbi.nlm.nih.gov/pubmed/22650647> (2012)

⁵⁷⁶ <http://www.ncbi.nlm.nih.gov/pubmed/22152626> (2012)

⁵⁷⁷ <http://www.ncbi.nlm.nih.gov/pubmed/22094553> (2011)

⁵⁷⁸ <http://www.ncbi.nlm.nih.gov/pubmed/21519220> (2011)

⁵⁷⁹ <http://www.ncbi.nlm.nih.gov/pubmed/20478402> (2010)

⁵⁸⁰ <http://www.ncbi.nlm.nih.gov/pubmed/19112401> (2008)

⁵⁸¹ <http://www.ncbi.nlm.nih.gov/pubmed/21982120> (2011)

⁵⁸² <http://www.ncbi.nlm.nih.gov/pubmed/10071523> (1999)

⁵⁸³ <http://www.ncbi.nlm.nih.gov/pubmed/15377055> (2004)

⁵⁸⁴ <http://www.ncbi.nlm.nih.gov/pubmed/22516851> (2012)

⁵⁸⁵ <http://www.ncbi.nlm.nih.gov/pubmed/15377055> (2004)

⁵⁸⁶ <http://www.ncbi.nlm.nih.gov/pubmed/10071523> (1999)

⁵⁸⁷ <http://www.ncbi.nlm.nih.gov/pubmed/20447621> (2010)

⁵⁸⁸ <http://www.ncbi.nlm.nih.gov/pubmed/19929573> (2010)

⁵⁸⁹ <http://www.ncbi.nlm.nih.gov/pubmed/18569389> (2008)

⁵⁹⁰ <http://www.ncbi.nlm.nih.gov/pubmed/18971533> (2008)

- cleaves cross-linked fibrin⁵⁹²
- Increased activated factor VII levels⁵⁹³
- inactivates plasminogen activator inhibitor type 1 and then potentiates fibrinolytic activity⁵⁹⁴
- Maximum dosage: 4000 Fibrin Units^{595 596}

11.1.31 Niacin

11.1.32 Olive Leaf Extract

Olive Leaf (Oleuropein) has antioxidant, antihypertensive, antiatherogenic, anti-inflammatory, hypoglycemic, and hypocholesterolemic properties⁵⁹⁷

- Anti-viral activity^{598 599 600 601}
- Increases IAP1 and IAP2⁶⁰²
- Acts on gp-41 pathway⁶⁰³
- Interactions with viral envelope⁶⁰⁴

11.1.33 Omega-3

Omega 3 includes Eicosapentaenoic acid

- Omega-3/Omega-6 ratio lower in CFS patients⁶⁰⁵
- Omega-3 helped (single case report)⁶⁰⁶
- Reduces TNF-alpha⁶⁰⁷ but not CRP⁶⁰⁸

11.1.34 Prednisone

Used to moderate JHR⁶⁰⁹.

⁵⁹¹ <http://www.ncbi.nlm.nih.gov/pubmed/16899918> (2006)

⁵⁹² <http://www.ncbi.nlm.nih.gov/pubmed/8593442> (1995)

⁵⁹³ <http://www.ncbi.nlm.nih.gov/pubmed/9491273> (1997)

⁵⁹⁴ <http://www.ncbi.nlm.nih.gov/pubmed/12850244> (2003)

⁵⁹⁵ http://www.pureprescriptions.com/expert_opinion/Nattokinase-Information.asp

⁵⁹⁶ <http://digitalnaturopath.com/treat/T447441.html>

⁵⁹⁷ <http://www.ncbi.nlm.nih.gov/pubmed/19906250> (2009)

⁵⁹⁸ <http://www.ncbi.nlm.nih.gov/pubmed/17537437> (2007)

⁵⁹⁹ <http://www.ncbi.nlm.nih.gov/pubmed/12878215> (2003)

⁶⁰⁰ <http://www.ncbi.nlm.nih.gov/pubmed/17275783> (2003)

⁶⁰¹ <http://www.ncbi.nlm.nih.gov/pubmed/15869811> (2005)

⁶⁰² <http://www.ncbi.nlm.nih.gov/pubmed/12878215> (2003)

⁶⁰³ <http://www.ncbi.nlm.nih.gov/pubmed/17537437> (2007)

⁶⁰⁴ <http://www.ncbi.nlm.nih.gov/pubmed/15869811> (2005)

⁶⁰⁵ <http://www.ncbi.nlm.nih.gov/pubmed/16380690> (2005)

⁶⁰⁶ <http://www.ncbi.nlm.nih.gov/pubmed/15117099> (2004)

⁶⁰⁷ <http://www.ncbi.nlm.nih.gov/pubmed/22224257> (2011)

⁶⁰⁸ <http://www.ncbi.nlm.nih.gov/pubmed/22569435> (2012)

⁶⁰⁹ http://www.cpnhelp.org/emerging_stratton_protocol

See <http://en.wikipedia.org/wiki/Prednisone>

11.1.35 Racetams

The modes of action of piracetam and most of its derivatives remain an enigma but appear to have an effect on glutamate receptors. Divided into subgroups:

- piracetam, oxiracetam, aniracetam, pramiracetam and phenylpiracetam
 - Improved cognitive deficits/disabilities
 - Neuroprotective effects
 - Lowering depression and anxiety
 - Vasodilator
- levetiracetam, seletracetam and brivaracetam
 - antiepileptic activity
 - cognitive effects uncertain

Includes Piracetam, Levetiracetam

- Piracetam corrects vegetative and psychoemotional disorders⁶¹⁰

The random administration of four different single oral doses of piracetam (Nootropil, CAS 7491-74-9)-- 1.6 g, 3.2 g, 4.8 g and 9.6 g--at fixed intervals of 2 weeks to 5 healthy subjects has confirmed and explicated its platelet anti-aggregant and rheological properties after doses of 4.8 g and 9.6 g. The effect on platelet aggregation occurs through inhibition of thromboxane synthetase or anti-thromboxane A2 activity together with a reduction in the plasma level of von Willebrand's factor (F.VIII R:vW). The rheological effect is related to the action of piracetam on cell membrane deformability (red cells, white cells and platelets) and to its simultaneous effect in reducing by 30-40% plasma levels of fibrinogen and von Willebrand's factor. In addition, it exerts a direct stimulant effect on prostacyclin synthesis in healthy endothelium. These effects are greatest between 1 and 4 h after dosage, and then diminish progressively to disappear between 8 and 12 h after administration. This explains the need to divide the total daily dose into 3 intakes at 8-hourly intervals. This study confirms the presence of four sites of action of piracetam: the vessel wall, platelets, plasma and cell membranes (RBC, WBC), which provide the basis for the potentially important antithrombotic activity of piracetam.⁶¹¹

- Reduces IL1-beta⁶¹², TNF-alpha, IL-8⁶¹³

For coagulation⁶¹⁴, reduces

- von Willebrand's factor
- inhibition of thromboxane synthetase
- inhibition of anti-thromboxane A2
- 30-40% reduction in plasma levels of fibrinogen

⁶¹⁰ <http://www.ncbi.nlm.nih.gov/pubmed/11855320> (2002)

⁶¹¹ <http://www.ncbi.nlm.nih.gov/pubmed/8457235> (1993)

⁶¹² <http://www.ncbi.nlm.nih.gov/pubmed/20080147> (2010)

⁶¹³ <http://www.ncbi.nlm.nih.gov/pubmed/17311542> (2007)

⁶¹⁴ <http://www.ncbi.nlm.nih.gov/pubmed/8457235> (1993)

- reduces cell membrane deformability (red cells, white cells and platelets)

11.1.36 **R Lipoic Acid**

See Alpha Lipoic Acid.

11.1.37 **Serrapeptase**

- Antiinflammatory^{615 616 617}
- Improves antibiotic concentration up to 850%^{618 619}
- Inhibits the formation of biofilms^{620 621}
- Effective for inflammatory venous disease⁶²²
- Maximum dosage: 40,000⁶²³

11.1.38 **Sunflower Oil**

- Increases in fibrinogen, factor VII, vWF, triglycerides, and cholesterol and a significant decrease in high-density lipoprotein⁶²⁴.

11.1.39 **Taurine**

- Inhibits s IL-1 and IL-6⁶²⁵, TNF-alpha⁶²⁶
- inhibits production of TGF-beta, a major fibrogenic cytokine⁶²⁷

11.1.40 **Transfer Factor**

Transfer factor is

11.1.41 **Turmeric**

The active ingredient of this kitchen spice is curcumin. Turmeric appears to be more effective than curcumin, the extract⁶²⁸.

- Reduces IL6, IL8⁶²⁹, TNF-alpha⁶³⁰
- Increases fibrinolytic activity⁶³¹

⁶¹⁵ <http://www.ncbi.nlm.nih.gov/pubmed/20582192> (2010)

⁶¹⁶ <http://www.ncbi.nlm.nih.gov/pubmed/20390096> (2008)

⁶¹⁷ <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3043339/?tool=pubmed> (2010)

⁶¹⁸ <http://www.ncbi.nlm.nih.gov/pubmed/7001087> (1980)

⁶¹⁹ <http://www.ncbi.nlm.nih.gov/pubmed/18479885> (2008)

⁶²⁰ <http://www.ncbi.nlm.nih.gov/pubmed/21978698> (2011)

⁶²¹ <http://www.ncbi.nlm.nih.gov/pubmed/18479885> (2008)

⁶²²⁶²² <http://www.ncbi.nlm.nih.gov/pubmed/9091835> (1996)

⁶²³ <http://stevensponaaglewordpress.com/?p=1146>

⁶²⁴ <http://www.ncbi.nlm.nih.gov/pubmed/11474472> (2001)

⁶²⁵ <http://www.ncbi.nlm.nih.gov/pubmed/20430256> (2010)

⁶²⁶ <http://www.ncbi.nlm.nih.gov/pubmed/21637907> (2011)

⁶²⁷ <http://www.ncbi.nlm.nih.gov/pubmed/20430256> (2010)

⁶²⁸ <http://www.ncbi.nlm.nih.gov/pubmed/22079310> (2012)

⁶²⁹ <http://www.ncbi.nlm.nih.gov/pubmed/22183741> (2011)

⁶³⁰ <http://www.ncbi.nlm.nih.gov/pubmed/22554269> (2012)

⁶³¹ <http://www.ncbi.nlm.nih.gov/pubmed/21071923> (2010)

- Reduces high level of fibrinogen⁶³²
- Inhibit platelet aggregation, increases coagulation. time⁶³³

11.1.42 Ubiquinol

See Coenzyme Q10

11.1.43 Vitamin-C

- Used by [ChPn]⁶³⁴

11.1.44 Vitamin-D

- 22% of CFS patients are deficient (≤ 20 ng/mL)⁶³⁵
- 61%⁶³⁶ - 70%⁶³⁷ - 80%⁶³⁸ of FM patients are deficient (≤ 20 ng/mL)
- Moderately to severely suboptimal in CFS patients⁶³⁹
- Associated with orthostatic intolerance⁶⁴⁰
- Associated with headaches, hypersomnia⁶⁴¹
- Treatment with high-dose vitamin D resulted in clinical improvement in all patients⁶⁴².
 - improvement became more significant when their blood level of 25(OH) D exceeded 50 ng/ mL⁶⁴³.
- Patients with 25-OHD ≤ 20 ng/ml are more likely to have ⁶⁴⁴
 - impaired short memory
 - confusion
 - mood disturbance
 - sleep disturbance
 - restless leg syndrome
 - palpitation
- Levels in FM patients and non-FM patients were not different in some studies^{645 646 647 648}.
- With myalgia in statin-treated patients, 92% were resolved when levels reached 50 ng/mL⁶⁴⁹

⁶³² <http://www.ncbi.nlm.nih.gov/pubmed/10802125> (2000)

⁶³³ <http://www.ncbi.nlm.nih.gov/pubmed/12575127> (2000)

⁶³⁴ <http://chlamydia-pneumoniae.org/treatment.html>

⁶³⁵ <http://www.ncbi.nlm.nih.gov/pubmed/21886073> (2011)

⁶³⁶ <http://www.ncbi.nlm.nih.gov/pubmed/21894355> (2011)

⁶³⁷ <http://www.ncbi.nlm.nih.gov/pubmed/16850115> (2007)

⁶³⁸ <http://www.ncbi.nlm.nih.gov/pubmed/21375201> (2010)

⁶³⁹ <http://www.ncbi.nlm.nih.gov/pubmed/20209476> (2009)

⁶⁴⁰ <http://www.ncbi.nlm.nih.gov/pubmed/21886073> (2011)

⁶⁴¹ <http://www.ncbi.nlm.nih.gov/pubmed/21206551> (2010)

⁶⁴² <http://www.ncbi.nlm.nih.gov/pubmed/22221390> (2012)

⁶⁴³ <http://www.ncbi.nlm.nih.gov/pubmed/21894355> (2011)

⁶⁴⁴ <http://www.ncbi.nlm.nih.gov/pubmed/22311432> (2012)

⁶⁴⁵ <http://www.ncbi.nlm.nih.gov/pubmed/21384747> (2010)

⁶⁴⁶ <http://www.ncbi.nlm.nih.gov/pubmed/19697583> (2009)

⁶⁴⁷ <http://www.ncbi.nlm.nih.gov/pubmed/21384747> (2010)

⁶⁴⁸ <http://www.ncbi.nlm.nih.gov/pubmed/18431091> (2008)

⁶⁴⁹ <http://www.ncbi.nlm.nih.gov/pubmed/19100953> (2009)

Comment: a level of 50+ ng/mL appears to be a critical threshold for improvement, this is the level where parathyroid hormone stimulation occurs.

11.1.45 Wobenzym

A combination of Bromelain with other enzymes.

- Increased TNF-alpha and IL-6⁶⁵⁰
- Increases TNF-alpha, IL-1 beta and IL-6⁶⁵¹
- Used by [ChPn]⁶⁵²

IMHO: Do not use.

11.2 Antiviral

11.2.1 Valacyclovir

Active against most species of the herpes virus family.

- Improves EBV only infection^{653 654}
- No impact on EBV+CMV⁶⁵⁵
- No known neuroprotective effects.

11.3 Antibacterial

There are several protocols circulating for the treatment of CFS and related conditions. The antibiotics that are seen in the various protocols are annotated in the details of each antibiotic. The three most explored chronic infections are for: Lyme, Chlamydia-Pneumonia and Rickettsia.

- [Jadin] - Dr. C. Jadin: Protocol for Rickettsia Like infections
- [ChPn] – see <http://chlamydia-pneumoniae.org> and
- [ChPH] – see <http://www.cpnhelp.org/>
- [Statton] – see http://www.cpnhelp.org/emerging_stratton_protoco

When looking at antibiotics, I deem the following to be important for CFS:

- Ability to reach the brain^{656 657}

⁶⁵⁰ <http://www.ncbi.nlm.nih.gov/pubmed/7529614> (1994)

⁶⁵¹ <http://www.ncbi.nlm.nih.gov/pubmed/7694216> (1993)

⁶⁵² <http://chlamydia-pneumoniae.org/treatment.html>

⁶⁵³ <http://www.ncbi.nlm.nih.gov/pubmed/12582420> (2002)

⁶⁵⁴ <http://www.ncbi.nlm.nih.gov/pubmed/18019402> (2007)

⁶⁵⁵ <http://www.ncbi.nlm.nih.gov/pubmed/12582420> (2002)

- Neuroprotective characteristics⁶⁵⁸
- Anticoagulant characteristics
- Anti-inflammatory characteristics
- Infections that it is effective against (and how effective)

There are other factors, such as risk of adverse reactions, cost, etc. which may be factors that MDs may need to take into consideration.

11.3.1 Aminoglycoside Antibiotics

11.3.1.1 *Kanamycin*

- Used with Japan Outbreak⁶⁵⁹
- No known neuroprotective effects.

11.3.2 Beta-lactam antibiotics

- First choice for high-risk pneumoniae⁶⁶⁰
- Neuroprotective effects^{661 662 663 664 665}
 - Increases glutamate transporter expression by gene activation⁶⁶⁶
- Family of antibiotics used by Dr. Jadin
- May induce vitamin K deficiency/ warfarin interactions^{667 668 669 670}
- Inhibit platelet function⁶⁷¹

11.3.2.1 *Amoxicillin*

- First choice for typical pneumoniae^{672 673}, 87% effective⁶⁷⁴
- No known neuroprotective effects.
- Effective for mycoplasma pneumoniae and chlamydia pneumoniae⁶⁷⁵

⁶⁵⁶ <http://www.ncbi.nlm.nih.gov/pubmed/22745353> (2012)

⁶⁵⁷ <http://www.ncbi.nlm.nih.gov/pubmed/21438200> (2010)

⁶⁵⁸ <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC548404/?tool=pubmed> (2005)

⁶⁵⁹ <http://www.ncbi.nlm.nih.gov/pubmed/16634532> (2006)

⁶⁶⁰ <http://www.ncbi.nlm.nih.gov/pubmed/16607488> (2006)

⁶⁶¹ <http://www.ncbi.nlm.nih.gov/pubmed/21933448> (2011)

⁶⁶² <http://www.ncbi.nlm.nih.gov/pubmed/21693120> (2011)

⁶⁶³ <http://www.ncbi.nlm.nih.gov/pubmed/21295027> (2011)

⁶⁶⁴ <http://www.ncbi.nlm.nih.gov/pubmed/17363173> (2007)

⁶⁶⁵ <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC548404/?tool=pubmed> (2005)

⁶⁶⁶ <http://www.ncbi.nlm.nih.gov/pubmed/15635412> (2005)

⁶⁶⁷ <http://www.ncbi.nlm.nih.gov/pubmed/21856805> (2011)

⁶⁶⁸ <http://www.ncbi.nlm.nih.gov/pubmed/17896903> (2007)

⁶⁶⁹ <http://www.ncbi.nlm.nih.gov/pubmed/17163280> (2006)

⁶⁷⁰ <http://www.ncbi.nlm.nih.gov/pubmed/16369967> (2006)

⁶⁷¹ <http://www.ncbi.nlm.nih.gov/pubmed/20663153> (2010)

⁶⁷² <http://www.ncbi.nlm.nih.gov/pubmed/17508663> (2007)

⁶⁷³ <http://www.ncbi.nlm.nih.gov/pubmed/16607488> (2006)

⁶⁷⁴ <http://www.ncbi.nlm.nih.gov/pubmed/16181747> (2005)

⁶⁷⁵ <http://www.ncbi.nlm.nih.gov/pubmed/11214557> (1998)

- Effective for Lyme
 - Reduced spirochetal forms by ~85%-90% and round body forms by ~68%⁶⁷⁶
 - Effective with concentration of (3.2mg/ml)^{677 678}

11.3.2.2 Cefotaxime

- In vitro for Lyme, required concentration (> 0.125 mg/L) ^{679 680}

11.3.2.3 Ceftriaxone

- Adverse reactions known⁶⁸¹.
- Crosses a inflamed blood-brain barrier⁶⁸²
- In vitro for Lyme, required concentration (> 0.03 mg/L) ^{683 684 685 686}

11.3.2.4 Cefuroxime

- Effective for Lyme⁶⁸⁷
- Can cross the blood-brain-barrier⁶⁸⁸
- In vitro for Lyme, required concentration (> 0.25 mg/L) ^{689 690}

11.3.2.5 Cefoperazone

- Effective for Lyme^{691 692}

11.3.3 Fluoroquinolone

- Family of antibiotics used by Dr. Jadin
- Uncertain neuroprotective effects⁶⁹³

11.3.3.1 Levofloxacin

- Effective for pneumonias⁶⁹⁴ (500-1000 mg/day)
- 250-750 mg x 1/day: [ChPn⁶⁹⁵]

⁶⁷⁶ <http://www.ncbi.nlm.nih.gov/pubmed/21753890> (2011)

⁶⁷⁷ <http://www.ncbi.nlm.nih.gov/pubmed/2073103> (1990)

⁶⁷⁸ <http://www.ncbi.nlm.nih.gov/pubmed/8852472> (1996)

⁶⁷⁹ <http://www.ncbi.nlm.nih.gov/pubmed/21771509> (2010)

⁶⁸⁰ <http://www.ncbi.nlm.nih.gov/pubmed/8852472> (1996)

⁶⁸¹ <http://www.ncbi.nlm.nih.gov/pubmed/21969285> (2011)

⁶⁸² <http://www.ncbi.nlm.nih.gov/pubmed/20503158> (2010)

⁶⁸³ <http://www.ncbi.nlm.nih.gov/pubmed/21771509> (2010)

⁶⁸⁴ <http://www.ncbi.nlm.nih.gov/pubmed/2073103> (1990)

⁶⁸⁵ <http://www.ncbi.nlm.nih.gov/pubmed/3566246> (1987)

⁶⁸⁶ <http://www.ncbi.nlm.nih.gov/pubmed/8852472> (1996)

⁶⁸⁷ <http://www.ncbi.nlm.nih.gov/pubmed/17412541> (2007)

⁶⁸⁸ <http://en.wikipedia.org/wiki/Cefuroxime>

⁶⁸⁹ <http://www.ncbi.nlm.nih.gov/pubmed/21771509> (2010)

⁶⁹⁰ <http://www.ncbi.nlm.nih.gov/pubmed/2073103> (1990)

⁶⁹¹ <http://www.ncbi.nlm.nih.gov/pubmed/9158807> (1995)

⁶⁹² <http://www.ncbi.nlm.nih.gov/pubmed/17412541> (2007)

⁶⁹³ <http://www.ncbi.nlm.nih.gov/pubmed/21387379> (2011)

⁶⁹⁴ <http://www.ncbi.nlm.nih.gov/pubmed/16163420> (2005)

11.3.3.2 ***Moxifloxacin***

- Effective for pneumonias^{696 697} (400 mg/day)
- Better penetration than gatifloxacin or levofloxacin⁶⁹⁸

11.3.3.3 ***Ofloxacin***

See <http://en.wikipedia.org/wiki/Ofloxacin>

- Effective for chlamydia pneumoniae⁶⁹⁹ (400 mg/day)

11.3.4 ***MAacrolide antibiotic***

- Family of antibiotics used [Jadin], [Statton⁷⁰⁰]
- One (rapamycin^{701 702 703}) has neuroprotective effect and crosses into the brain⁷⁰⁴.
- First choice for Mycoplasma pneumoniae or Chlamydia pneumoniae⁷⁰⁵
- First choice for high-risk pneumonias⁷⁰⁶

11.3.4.1 ***Azithromycin***

- 250-500 mg x 1/day: [ChPn⁷⁰⁷]⁷⁰⁸
- Effective against pneumonias 94%⁷⁰⁹
- Decreases symptoms in CFS⁷¹⁰ (60%)
 - a. Reduced l-Carnitine levels
- Effective for mycoplasma pneumoniae and chlamydia pneumoniae⁷¹¹
- Effective for Lyme: 96%^{712 713 714}
- Effective for Chlamydia infections⁷¹⁵
- 500mg

⁶⁹⁵ <http://chlamydia-pneumoniae.org/treatment.html>

⁶⁹⁶ <http://www.ncbi.nlm.nih.gov/pubmed/16163420> (2005)

⁶⁹⁷ <http://chlamydia-pneumoniae.org/treatment.html>

⁶⁹⁸ <http://www.ncbi.nlm.nih.gov/pubmed/22529026> (2012)

⁶⁹⁹ <http://chlamydia-pneumoniae.org/treatment.html>

⁷⁰⁰ http://www.cpnhelp.org/emerging_stratton_protocol

⁷⁰¹ <http://www.ncbi.nlm.nih.gov/pubmed/21772323> (2011)

⁷⁰² <http://www.ncbi.nlm.nih.gov/pubmed/20849946> (2011)

⁷⁰³ <http://www.ncbi.nlm.nih.gov/pubmed/21447003> (2011)

⁷⁰⁴ <http://www.ncbi.nlm.nih.gov/pubmed/22264993> (2012)

⁷⁰⁵ <http://www.ncbi.nlm.nih.gov/pubmed/17508663> (2007)

⁷⁰⁶ <http://www.ncbi.nlm.nih.gov/pubmed/16607488> (2006)

⁷⁰⁷ <http://chlamydia-pneumoniae.org/treatment.html>

⁷⁰⁸ <http://www.ncbi.nlm.nih.gov/pubmed/16163420> (2005)

⁷⁰⁹ <http://www.ncbi.nlm.nih.gov/pubmed/9692520> (1998)

⁷¹⁰ <http://www.translational-medicine.com/content/4/1/34/>

⁷¹¹ <http://www.ncbi.nlm.nih.gov/pubmed/11214557> (1998)

⁷¹² <http://www.ncbi.nlm.nih.gov/pubmed/10879639> (2000)

⁷¹³ <http://www.ncbi.nlm.nih.gov/pubmed/2154436> (1990)

⁷¹⁴ <http://www.ncbi.nlm.nih.gov/pubmed/8852472> (1996)

⁷¹⁵ <http://www.ncbi.nlm.nih.gov/pubmed/16669564> (2006)

11.3.4.2 *Clarithromycin*

- Higher dosages are more effective against mycoplasma pneumoniae⁷¹⁶
- 500 mg x 2/day: [ChPn⁷¹⁷] ⁷¹⁸
- Effective against pneumonias 70%⁷¹⁹

11.3.4.3 *Erythromycin*

- Used with Japan Outbreak⁷²⁰
- Effective for mycoplasma pneumoniae and chlamydia pneumoniae⁷²¹
- Effective with concentration of (0.32mg/ml)^{722 723 724}
- 500 mg QID⁷²⁵

11.3.4.4 *Josamycin*

See <http://en.wikipedia.org/wiki/Josamycin>

- 1000 mg x 2/day: [ChPn⁷²⁶]

11.3.4.5 *Rapamycin*

See <http://en.wikipedia.org/wiki/Sirolimus>

- Neuroprotective⁷²⁷
- Effective for Crohn's⁷²⁸

11.3.4.6 *Roxithromycin*

- 300 mg x 1-2/day: [ChPn⁷²⁹]
- Partially effective for Lyme⁷³⁰

11.3.4.7 *Sparfloxacin*

See <http://en.wikipedia.org/wiki/Sparfloxacin>

- 200 mg x 1/day: [ChPn⁷³¹]

⁷¹⁶ <http://www.ncbi.nlm.nih.gov/pubmed/21791441> (2011)

⁷¹⁷ <http://chlamydia-pneumoniae.org/treatment.html>

⁷¹⁸ <http://www.ncbi.nlm.nih.gov/pubmed/16163420> (2005)

⁷¹⁹ <http://www.ncbi.nlm.nih.gov/pubmed/9692520> (1998)

⁷²⁰ <http://www.ncbi.nlm.nih.gov/pubmed/16634532> (2006)

⁷²¹ <http://www.ncbi.nlm.nih.gov/pubmed/11214557> (1998)

⁷²² <http://www.ncbi.nlm.nih.gov/pubmed/2073103> (1990)

⁷²³ <http://www.ncbi.nlm.nih.gov/pubmed/3566246> (1987)

⁷²⁴ <http://www.ncbi.nlm.nih.gov/pubmed/3566246> (1987)

⁷²⁵ <http://www.ncbi.nlm.nih.gov/pubmed/16163420> (2005)

⁷²⁶ <http://chlamydia-pneumoniae.org/treatment.html>

⁷²⁷ <http://www.ncbi.nlm.nih.gov/pubmed/21772323> (2011)

⁷²⁸ <http://www.ncbi.nlm.nih.gov/pubmed/18719139> (2008)

⁷²⁹ <http://chlamydia-pneumoniae.org/treatment.html>

⁷³⁰ <http://www.ncbi.nlm.nih.gov/pubmed/8852472> (1996)

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11.3.5 Rifamycin

- Family of antibiotics used by [Statton⁷³²]

11.3.5.1 Rifabutin

See <http://en.wikipedia.org/wiki/Rifabutin>

- Used for Crohn's Disease^{733 734}, being tried for IBS

11.3.5.2 Rifampicin

See <http://en.wikipedia.org/wiki/Rifampin>

- Used for Crohn's Disease⁷³⁵

11.3.5.3 Rifaximin

See <http://en.wikipedia.org/wiki/Rifaximin>

- Used for Irritable Bowel Syndrome (IBS)⁷³⁶

11.3.6 Tetracyclines

- Tetracyclines has the anti-inflammatory, antihypernociceptive and neuroprotective activities⁷³⁷
- Oxygen radical scavengers and anti-inflammatory agents⁷³⁸.
- Minocycline is most studied for neuroprotective effects⁷³⁹.
- Highly effective against various pathogens including rickettsiae, Gram-positive, and Gram-negative bacteria⁷⁴⁰.
- Family of antibiotics used by [Jadin], [Statton⁷⁴¹]
- Tetracyclines moderate inflammatory responses of various etiologies⁷⁴²

11.3.6.1 Doxycycline

- Antiprotease activities⁷⁴³
- Effective for Lyme: 83%^{744 745 746 747}

⁷³¹ <http://chlamydia-pneumoniae.org/treatment.html>

⁷³² http://www.cpnhelp.org/emerging_stratton_protocol

⁷³³ <http://www.ncbi.nlm.nih.gov/pubmed/17570206> (2007)

⁷³⁴ <http://www.ncbi.nlm.nih.gov/pubmed/11930899> (2002)

⁷³⁵ <http://www.ncbi.nlm.nih.gov/pubmed/8147352> (1994)

⁷³⁶ <http://www.ncbi.nlm.nih.gov/pubmed/21488771> (2011)

⁷³⁷ <http://www.ncbi.nlm.nih.gov/pubmed/22282331> (2012)

⁷³⁸ <http://www.ncbi.nlm.nih.gov/pubmed/20592239> (2010)

⁷³⁹ <http://www.ncbi.nlm.nih.gov/pubmed/21985758> (2011)

⁷⁴⁰ <http://www.ncbi.nlm.nih.gov/pubmed/20592239> (2010)

⁷⁴¹ http://www.cpnhelp.org/emerging_stratton_protocol

⁷⁴² <http://www.ncbi.nlm.nih.gov/pubmed/19301981> (2009)

⁷⁴³ <http://www.ncbi.nlm.nih.gov/pubmed/20592239> (2010)

- Reduced spirochetal structures ~90% but increased the number of round body forms about twofold⁷⁴⁸.
- Effective with concentration of (1.6mg/ml)⁷⁴⁹
- 100 mg @ 2/day for 6-12 weeks [ChPn]
- Effective for Chlamydia infections⁷⁵⁰
- In vitro for Lyme, required concentration (> 0.25 mg/L) ⁷⁵¹
- Reduced the production of tumor necrosis factor-alpha, interleukin (IL)-6, and IL-8⁷⁵²

11.3.6.2 Minocycline

- Neuroprotective⁷⁵³
 - Reduces gray and white matter injury^{754 755 756}
 - Better penetration with aspirin⁷⁵⁷
 - Cross the blood-brain barrier to the greatest extent of all tetracyclines⁷⁵⁸
 - Improves more issues than doxycycline⁷⁵⁹
- Reduced the production of tumor necrosis factor-alpha, interleukin (IL)-6, and IL-8⁷⁶⁰
- Readily cross cell membranes, is known to be a potent anti-apoptotic agent⁷⁶¹.
- Effective for Coxiella Burnetii^{762 763}
 - 100 mg/day for 3 months

11.3.6.3 Tetracycline

- In vitro for Lyme, required concentration (> 0.25 mg/L) ⁷⁶⁴
- Effective with concentration of (3.2mg/ml)^{765 766 767}

⁷⁴⁴ <http://www.ncbi.nlm.nih.gov/pubmed/10879639> (2000)

⁷⁴⁵ <http://www.ncbi.nlm.nih.gov/pubmed/21969285> (2011)

⁷⁴⁶ <http://www.ncbi.nlm.nih.gov/pubmed/21929779> (2011)

⁷⁴⁷ <http://www.ncbi.nlm.nih.gov/pubmed/8852472> (1996)

⁷⁴⁸ <http://www.ncbi.nlm.nih.gov/pubmed/21753890> (2011 *)

⁷⁴⁹ <http://www.ncbi.nlm.nih.gov/pubmed/2073103> (1990)

⁷⁵⁰ <http://www.ncbi.nlm.nih.gov/pubmed/16669564> (2006)

⁷⁵¹ <http://www.ncbi.nlm.nih.gov/pubmed/21771509> (2010)

⁷⁵² <http://www.ncbi.nlm.nih.gov/pubmed/19301981> (2009)

⁷⁵³ <http://www.ncbi.nlm.nih.gov/pubmed/22414722>, for many more,

<http://www.ncbi.nlm.nih.gov/pubmed?term=Neuroprotective%20minocycline>

⁷⁵⁴ <http://www.ncbi.nlm.nih.gov/pubmed/22763274> (2012)

⁷⁵⁵ <http://www.ncbi.nlm.nih.gov/pubmed/21304434> (2011)

⁷⁵⁶ <http://www.ncbi.nlm.nih.gov/pubmed/16871064> (2006)

⁷⁵⁷ <http://www.ncbi.nlm.nih.gov/pubmed/22045867> (2012)

⁷⁵⁸ <http://www.ncbi.nlm.nih.gov/pubmed/22282331> (2012)

⁷⁵⁹ <http://www.ncbi.nlm.nih.gov/pubmed/17719028> (2007)

⁷⁶⁰ <http://www.ncbi.nlm.nih.gov/pubmed/19301981> (2009)

⁷⁶¹ <http://www.ncbi.nlm.nih.gov/pubmed/20592239> (2010)

⁷⁶² <http://www.ncbi.nlm.nih.gov/pubmed/16415546> (2005)

⁷⁶³ <http://www.ncbi.nlm.nih.gov/pubmed/14964579> (2004)

⁷⁶⁴ <http://www.ncbi.nlm.nih.gov/pubmed/21771509> (2010)

⁷⁶⁵ <http://www.ncbi.nlm.nih.gov/pubmed/2073103> (1990)

11.3.6.4 Tigecycline

Also known as glycylicline.

- In vitro for Lyme⁷⁶⁸, required least concentration (< 0.016 mg/L)⁷⁶⁹
 - Reduced both spirochetal and round body forms by ~80%-90%⁷⁷⁰.
- Ineffective against persistent Lyme⁷⁷¹
- Half-life of 36 hour⁷⁷²
- Successfully evaded most bacterial resistance mechanisms⁷⁷³

11.4 Anticoagulants

11.4.1 Heparin

Low dose heparin therapy decreases thrombin generation and soluble fibrin production, improves blood flow, allows for fibrinolysis to clean up fibrin deposition, and allows the return of an anticoagulant environment (instead of a procoagulant environment) in the capillaries⁷⁷⁴.

11.5 Anti-Parasitic Drugs

11.5.1 Tinidazole

- 500mg x 2pd: CPN-S, CPN-W
- Effective for Lyme
 - Reduced both spirochetal and round body forms by ~80%-90%⁷⁷⁵.
 - Reduced viable organisms by ~90%⁷⁷⁶ (other antibiotics much less).

11.5.2 Metronidazole

- 400mg x 3 pd: CPN-W
- 300-500 mg x 3 pd: CPN-S
- [Jadin], [Statton⁷⁷⁷]
- Effective for Lyme
 - Reduction of spirochetal structures by ~90% and round body forms by ~80%⁷⁷⁸.

⁷⁶⁶ <http://www.ncbi.nlm.nih.gov/pubmed/3566246> (1987)

⁷⁶⁷ <http://www.ncbi.nlm.nih.gov/pubmed/3566246> (1987)

⁷⁶⁸ <http://www.ncbi.nlm.nih.gov/pubmed/19843691> (2009)

⁷⁶⁹ <http://www.ncbi.nlm.nih.gov/pubmed/21771509> (2010)

⁷⁷⁰ <http://www.ncbi.nlm.nih.gov/pubmed/21753890> (2011)

⁷⁷¹ <http://www.ncbi.nlm.nih.gov/pubmed/19995919> (2010)

⁷⁷² <http://www.ncbi.nlm.nih.gov/pubmed/14723559> (2004)

⁷⁷³ <http://www.ncbi.nlm.nih.gov/pubmed/16499287> (2006)

⁷⁷⁴

⁷⁷⁵ <http://www.ncbi.nlm.nih.gov/pubmed/21753890> (2011)

⁷⁷⁶ <http://www.ncbi.nlm.nih.gov/pubmed/21753890> (2011)

⁷⁷⁷ http://www.cpnhelp.org/emerging_stratton_protoco

⁷⁷⁸ <http://www.ncbi.nlm.nih.gov/pubmed/21753890> (2011)

Transfer Factor:

Some take sublingual.

11.6 Arsenic Based

These has been used in veterinary practice for animals with CFS⁷⁷⁹ and on veterinaries⁷⁸⁰. The drugs include:

- Potassium Arsenite
- Sodium Thiacetarsamide

Isonicotinylhydrazine (INH)

- 300 mg QD: CPN-S

Kanamycin

- Used with Japan Outbreak⁷⁸¹

Rifampin / Rifaximin

- 150 mg BID
- 200 mg x 3 pd

12 Exercise

“Physical exercise leads to minor activation of blood coagulation, which appears to be balanced by a concomitant activation of the fibrinolytic system.”⁷⁸² The immune response of chronic fatigue syndrome patients to exhaustive exercise is not significantly different from that of healthy nonphysically active controls.⁷⁸³ CFS patients can perform home exercises five times a week with an initial duration of 5-15 min per exercise session. The exercise duration can be gradually increased up to 30 min⁷⁸⁴.

- CFS patients increased intramuscular acidosis and exhibited significant prolongation (almost 4-fold) of the time taken for blood pH to recover to baseline^{785 786}.

⁷⁷⁹ <http://www.ncbi.nlm.nih.gov/pubmed/15129582> (2001),
<http://www.ncbi.nlm.nih.gov/pubmed/11440190> (2001)
<http://www.ncbi.nlm.nih.gov/pubmed/12688127> (2003)

⁷⁸⁰ <http://www.ncbi.nlm.nih.gov/pubmed/11561958> (2001)

⁷⁸¹ <http://www.ncbi.nlm.nih.gov/pubmed/16634532> (2006)

⁷⁸² <http://www.ncbi.nlm.nih.gov/pubmed/15931620> (2005)

⁷⁸³ <http://www.ncbi.nlm.nih.gov/pubmed/10226888> (1999)

⁷⁸⁴ <http://www.ncbi.nlm.nih.gov/pubmed/22725992> (2012)

⁷⁸⁵ <http://www.ncbi.nlm.nih.gov/pubmed/21749371> (2012)

- VO(2max), HR(max), and the LT in CFS patients were not different from healthy sedentary individuals of a similar age⁷⁸⁷.
- CFS+FM had lower systolic blood pressure etc. than just CFS patients⁷⁸⁸
- CFS+FM had less cognitive issues than CFS patients post exercise⁷⁸⁹.
- Pain thresholds decreased following exercise, whereas they increased in healthy subjects^{790 791}.

12.1 Post Exertional Malaise

This symptom is not seen in all CFS patients and its presence or absence has been used to sub-type CFS⁷⁹². Exercise can severely impact patients for over 24 hours⁷⁹³. This increases with the severity of CFS⁷⁹⁴. This exertion is suspected to amplify pre-existing pathophysiological abnormalities (inflammation, immune dysfunction, oxidative and nitrosative stress, channelopathy, defective stress response mechanisms and a hypoactive hypothalamic-pituitary-adrenal axis⁷⁹⁵, ATP deficit⁷⁹⁶).

PEM is seen with higher concentration difficulties, greater subjective experience of infection, and higher levels of IL-1, TNF α , and neopterin⁷⁹⁷.

13 Speculations

13.1 Xenotropic Murine Leukemia Related Virus

Xenotropic murine leukemia related virus (XMRV) was a hot topic of research^{798 799} because it was found in a high number(67% - 87%⁸⁰⁰) of CFS patients from one laboratory. Subsequent attempts^{801 802 803} to validate this finding failed and laboratory contamination was confirmed.

⁷⁸⁶ <http://www.ncbi.nlm.nih.gov/pubmed/20433583> (2010)
⁷⁸⁷ <http://www.ncbi.nlm.nih.gov/pubmed/11782647> (2002)
⁷⁸⁸ <http://www.ncbi.nlm.nih.gov/pubmed/22157881> (2012)
⁷⁸⁹ <http://www.ncbi.nlm.nih.gov/pubmed/16177595> (2005)
⁷⁹⁰ <http://www.ncbi.nlm.nih.gov/pubmed/20412374> (2010)
⁷⁹¹ <http://www.ncbi.nlm.nih.gov/pubmed/20878051> (2010 *)
⁷⁹² <http://www.ncbi.nlm.nih.gov/pubmed/22521895> (2012)
⁷⁹³ <http://www.ncbi.nlm.nih.gov/pubmed/18441039> (2008)
⁷⁹⁴ <http://www.ncbi.nlm.nih.gov/pubmed/19513826> (2009)
⁷⁹⁵ <http://www.ncbi.nlm.nih.gov/pubmed/19855350> (2009)
⁷⁹⁶ <http://www.ncbi.nlm.nih.gov/pubmed/22718491> (2012)
⁷⁹⁷ <http://www.ncbi.nlm.nih.gov/pubmed/22521895> (2012)
⁷⁹⁸ <http://www.ncbi.nlm.nih.gov/pubmed/20517289> (2010)
⁷⁹⁹ <http://www.ncbi.nlm.nih.gov/pubmed/20425007> (2010)
⁸⁰⁰ <http://www.ncbi.nlm.nih.gov/pubmed/20798047> (2010)
⁸⁰¹ <http://www.ncbi.nlm.nih.gov/pubmed/22697086> (2012)
⁸⁰² <http://www.ncbi.nlm.nih.gov/pubmed/21551158> (2011)
⁸⁰³ <http://www.ncbi.nlm.nih.gov/pubmed/21543496> (2011)

13.2 Early Life Immune Insult

Developmental immunotoxicity (DIT) and a variety of similar speculation raises questions about early childhood exposure to infections, drugs and chemicals results in increased susceptibility of some people for various diseases, including CFS. This speculation includes childhood trauma as a risk factor^{804 805 806 807 808}.

14 Models

14.1 Hypoxia

14.2 Blood by the Numbers

There are some interesting facts about blood discovered for CFS suggesting a mechanical model for part of the process. What we know is:

- Objectively measured abnormalities of blood pressure variability in CFS⁸⁰⁹
- Lower blood pressure in sleep⁸¹⁰
- Lower blood pressure⁸¹¹
- Less and slower variability of blood pressure^{812 813}
- Lower total blood volume⁸¹⁴ (8% - 9%⁸¹⁵ - 15%⁸¹⁶ less), plasma volume (13%⁸¹⁷) and red blood cell volume (19%)^{818 819 820}.
- 35% lower peak oxygen consumption⁸²¹
- Significant decrease in red cell distribution width⁸²²
- Increased heart Rate^{823 824 825}, higher rates were more fatigued^{826 827}

⁸⁰⁴ <http://www.ncbi.nlm.nih.gov/pubmed/19124690> (2009)

⁸⁰⁵ <http://www.ncbi.nlm.nih.gov/pubmed/17088506> (2006)

⁸⁰⁶ <http://www.ncbi.nlm.nih.gov/pubmed/18336982> (2008)

⁸⁰⁷ <http://www.ncbi.nlm.nih.gov/pubmed/17456021> (2007)

⁸⁰⁸ <http://www.ncbi.nlm.nih.gov/pubmed/19404874> (2009)

⁸⁰⁹ <http://www.ncbi.nlm.nih.gov/pubmed/22670061> (2012)

⁸¹⁰ <http://www.ncbi.nlm.nih.gov/pubmed/21059182> (2011)

⁸¹¹ <http://www.ncbi.nlm.nih.gov/pubmed/19297309> (2009)

⁸¹² <http://www.ncbi.nlm.nih.gov/pubmed/22670061> (2012)

⁸¹³ <http://www.ncbi.nlm.nih.gov/pubmed/20890710> (2011)

⁸¹⁴ <http://www.ncbi.nlm.nih.gov/pubmed/19534728> (2009)

⁸¹⁵ <http://www.ncbi.nlm.nih.gov/pubmed/11748048> (2002 *)

⁸¹⁶ <http://www.ncbi.nlm.nih.gov/pubmed/19469714> (2009)

⁸¹⁷ <http://www.ncbi.nlm.nih.gov/pubmed/19469714> (2009)

⁸¹⁸ <http://www.ncbi.nlm.nih.gov/pubmed/19469714> (2009)

⁸¹⁹ <http://www.ncbi.nlm.nih.gov/pubmed/10910366> (2000)

⁸²⁰ <http://www.ncbi.nlm.nih.gov/pubmed/17720950> (2007)

⁸²¹ <http://www.ncbi.nlm.nih.gov/pubmed/11748048> (2002 *)

⁸²² <http://www.ncbi.nlm.nih.gov/pubmed/17720950> (2007 *)

- Reduced stroke (volume pumped)⁸²⁸
- Faster heart beat often seen⁸²⁹(especially with JHR⁸³⁰)
- Higher percentages of misshaped red blood cells⁸³¹
 - Impaired capillary blood flow.
 - Changed red cell shape populations
 - High values for flat blood-cells

These observations suggest a mechanical model of some mechanism that impedes blood flow resulting in smaller and possibly-damaged red blood cells. While the total blood volume may be less, the actual number of red-blood cells could be the same (1 cell volume x No of Cells = Total Blood Volume) because of the reduced size of each blood cell. The impeding of the blood flow results in the heart switching to a smaller stroke that happen more often (Stroke Volume x Heart Rate = Blood flow rate). This may be equivalent to a car going uphill: a driver will shift to a lower gear because of the resistance offered by the slope. The number of engine rotations will go up, miles per gallon will go down – similar to the response of the heart.

The question then arises as to what impedes the blood flow. Simpson⁸³² and O’Neill⁸³³ speculated in 2001 that it was caused by reduced blood capillary size. Possible causes of small capillary size are a combination of inflammation of the capillary due to infection and genetic predisposition to small size. At the same time, Berg found hyper-coagulation in a high percentage of CFS patients. Hyper-coagulation or thick blood results in a higher viscosity and thus more resistance to blood flow. Fibrinogen depleting agents reduce fibrinogen in blood plasma, reduce blood viscosity and hence increase blood flow⁸³⁴. The hyper-coagulation also produces fibrin fibers which could act like a sieve allowing only smaller or deformed blood cells to pass through. Both items may be occurring.

14.2.1 Explorations

- With coagulation and high viscosity, one could speculate that stroke risks would be higher. A study of non-CFS patients found these did not contribute to stroke risk⁸³⁵.
- Does blood viscosity impacts dilation in arteries? A study found that it does, dilation is altered⁸³⁶⁸³⁷ ⁸³⁸. As shear stress increases, the arteries dilate, as stress decreases, the arteries constrict⁸³⁹.

⁸²³ <http://www.ncbi.nlm.nih.gov/pubmed/11528333> (2001)

⁸²⁴ <http://www.ncbi.nlm.nih.gov/pubmed/21059182> (2011)

⁸²⁵ <http://www.ncbi.nlm.nih.gov/pubmed/12357281> (2002)

⁸²⁶ <http://www.ncbi.nlm.nih.gov/pubmed/17851136> (2007)

⁸²⁷ <http://www.ncbi.nlm.nih.gov/pubmed/21382927> (2011)

⁸²⁸ <http://www.ncbi.nlm.nih.gov/pubmed/12357281> (2002)

⁸²⁹ <http://www.ncbi.nlm.nih.gov/pubmed/17630594> (2007)

⁸³⁰ See Jarisch-Herxheimers Reaction

⁸³¹ <http://orthomolecular.org/library/jom/2001/pdf/2001-v16n03-p157.pdf>

⁸³² <http://cfdidsreport.com/Articles/researchers/lessimpson.htm>

⁸³³ <http://orthomolecular.org/library/jom/2001/pdf/2001-v16n03-p157.pdf>

⁸³⁴ <http://www.ncbi.nlm.nih.gov/pubmed/22419274> (2012)

⁸³⁵ <http://www.ncbi.nlm.nih.gov/pubmed/11916073> (2002)

⁸³⁶ <http://www.ncbi.nlm.nih.gov/pubmed/2328521> (1990)

⁸³⁷ <http://www.ncbi.nlm.nih.gov/pubmed/2611812> (1989)

- A 5-9% increase in the whole blood viscosity, caused impairment of the erythrocyte deformability and aggregation with the efficacy of oxygen transport to tissues was decreased by 4-7%.⁸⁴⁰
- The viscosity of red blood cells determines their life span⁸⁴¹
- Viscosity impacts the percentage of deformed cells⁸⁴² and may reduce hemoglobin up to 20%⁸⁴³
- Aluminum causes significant decreases in mean corpuscular volume (MCV), red blood cell (RBC) deformability at low shear stress levels⁸⁴⁴.

14.2.2 Predictions

Improvement should be seen with the following types of agents

14.2.2.1 Fibrin breakdown agents

- Ancrod – prescription - derived from snake venom
- Defibrase – prescription – derived from snake venom
- Bromelain
- Lumbrokinase
- Nattokinase

14.2.2.2 Lower Blood Viscosity Agents

- Alpha Lipoic Acid has a positive effect.

14.2.2.3 Vascular dilators agents

- Niacin
 - NADH

14.2.3 Future Studies

- Does the level of Aluminum correlate with changes of blood characteristics?

⁸³⁸ <http://www.ncbi.nlm.nih.gov/pubmed/17148940> (2007 *)

⁸³⁹ <http://www.ncbi.nlm.nih.gov/pubmed/8072845> (1994)

⁸⁴⁰ <http://www.ncbi.nlm.nih.gov/pubmed/21894763> (2011)

⁸⁴¹ <http://www.ncbi.nlm.nih.gov/pubmed/7367832> (1980)

⁸⁴² <http://www.ncbi.nlm.nih.gov/pubmed/4016189> (1985 *)

⁸⁴³ www.ncbi.nlm.nih.gov/pubmed/15095784 (2004)

⁸⁴⁴ <http://www.ncbi.nlm.nih.gov/pubmed/16721596> (2007)

15 Treatments

To date, no pharmacological agent has been reliably shown to be effective treatment for CFS⁸⁴⁵. Management strategies are therefore primarily directed at relief of symptoms and minimizing impediments to recovery.

15.1 Antibiotics

CFS has neuroinflammatory characteristics suggesting that the pathogen may be in the brain. A major concern is that because of the blood-brain barrier (BBB), current regimens of commonly used antibiotics might be inadequate. Some studies suggest that commonly used antibiotics do not reach a therapeutic concentration range in brain. Antibacterial agents from the same chemical group have significantly different penetration⁸⁴⁶. The choice of antibiotics is critical to eliminate the pathogen in the brain.

- Prophylaxis treatment with antibiotics effective for Lyme⁸⁴⁷

15.1.1 Dosages

Table 3 Antibiotics used for CFS and related pathogens is shown below

Antibiotic	Dosage
Amoxicillin	50 mg/kg/day in 3 intakes ⁸⁴⁸
Doxycycline	100 mg bid ^{849 850}
Cefuroxim axetil	500 mg twice daily ⁸⁵¹
Azithromycin	500 mg/day ^{852 853}

Table 3 Antibiotics used for CFS and related pathogens

⁸⁴⁵ <http://www.ncbi.nlm.nih.gov/pubmed/18537652> (2008)

⁸⁴⁶ <http://www.ncbi.nlm.nih.gov/pubmed/22745353> (2012)

⁸⁴⁷ <http://www.ncbi.nlm.nih.gov/pubmed/20012878> (2010)

⁸⁴⁸ <http://www.ncbi.nlm.nih.gov/pubmed/17412541> (2007)

⁸⁴⁹ <http://www.ncbi.nlm.nih.gov/pubmed/17412541> (2007)

⁸⁵⁰ <http://www.ncbi.nlm.nih.gov/pubmed/10879639> (2000)

⁸⁵¹ <http://www.ncbi.nlm.nih.gov/pubmed/17412541> (2007)

⁸⁵² <http://www.ncbi.nlm.nih.gov/pubmed/17412541> (2007)

⁸⁵³ <http://www.ncbi.nlm.nih.gov/pubmed/10879639> (2000)

15.2 Jarisch-Herxheimers Reaction

Jarisch-Herxheimer reaction (J-HR) is an acute febrile reaction which may complicate the initiation of an effective treatment against infections due to intracellular micro-organisms⁸⁵⁴. Antibiotics increase the bioavailability of endotoxin from Gram-negative bacteria⁸⁵⁵. The increase may be up to 20 fold more⁸⁵⁶.

Can include:

- not uncommon to confuse drug allergy with JHR⁸⁵⁷.
- caused by release of endotoxin-like material and cytokine elevation^{858 859 860}.
- delusional behavior, fever, rigors, tachycardia and hypoxia^{861 862 863}, complex visual and auditory hallucinations⁸⁶⁴
- tachycardia, hypotension, and thrombocytopenia, elevated serum cardiac troponin⁸⁶⁵
- developed disseminated intravascular coagulation⁸⁶⁶.
- acute rise in temperature, tachycardia, tachypnea, hypoxia, hypotension⁸⁶⁷
- feeling cold with worsening headache and chills⁸⁶⁸
- Associated with high titers⁸⁶⁹, high concentrations of TNF, IL-6, and IL-8^{870 871} up to 8 fold increase over pre-antibiotic levels⁸⁷².
- Increase of IgG and IgM by 4x⁸⁷³
- Rise in body temperature (1 C)⁸⁷⁴
- potentially lethal⁸⁷⁵
- Seen with tetracyclines and penicillin⁸⁷⁶, ciprofloxacin⁸⁷⁷, sulfamethoxazole-trimethoprim⁸⁷⁸.

⁸⁵⁴ <http://www.ncbi.nlm.nih.gov/pubmed/9733392> (1998)

⁸⁵⁵ <http://www.ncbi.nlm.nih.gov/pubmed/7619330> (1995)

⁸⁵⁶ <http://www.ncbi.nlm.nih.gov/pubmed/1445982> (1992)

⁸⁵⁷ <http://www.ncbi.nlm.nih.gov/pubmed/16288069> (2005)

⁸⁵⁸ <http://www.ncbi.nlm.nih.gov/pubmed/15896248> (2005)

⁸⁵⁹ <http://www.ncbi.nlm.nih.gov/pubmed/9733392> (1998)

⁸⁶⁰ <http://www.ncbi.nlm.nih.gov/pubmed/9511083> (1998)

⁸⁶¹ <http://www.ncbi.nlm.nih.gov/pubmed/22707695> (2012)

⁸⁶² <http://www.ncbi.nlm.nih.gov/pubmed/20664452> (2010)

⁸⁶³ <http://www.ncbi.nlm.nih.gov/pubmed/9610974> (1998)

⁸⁶⁴ <http://www.ncbi.nlm.nih.gov/pubmed/12604286> (2002)

⁸⁶⁵ <http://www.ncbi.nlm.nih.gov/pubmed/22567483> (2011 *)

⁸⁶⁶ <http://www.ncbi.nlm.nih.gov/pubmed/12182387> (2002)

⁸⁶⁷ <http://www.ncbi.nlm.nih.gov/pubmed/19040755> (2008 *)

⁸⁶⁸ <http://www.ncbi.nlm.nih.gov/pubmed/16288069> (2005)

⁸⁶⁹ <http://www.ncbi.nlm.nih.gov/pubmed/20825309> (2010)

⁸⁷⁰ <http://www.ncbi.nlm.nih.gov/pubmed/16455348> (2006)

⁸⁷¹ <http://www.ncbi.nlm.nih.gov/pubmed/9093599> (1997 *)

⁸⁷² <http://www.ncbi.nlm.nih.gov/pubmed/1569394> (1992)

⁸⁷³ <http://www.ncbi.nlm.nih.gov/pubmed/8508816> (1993)

⁸⁷⁴ <http://www.ncbi.nlm.nih.gov/pubmed/1569394> (1992)

⁸⁷⁵ <http://www.ncbi.nlm.nih.gov/pubmed/21803390> (2011)

⁸⁷⁶ <http://www.ncbi.nlm.nih.gov/pubmed/21803390> (2011)

⁸⁷⁷ <http://www.ncbi.nlm.nih.gov/pubmed/12182387> (2002)

⁸⁷⁸ <http://www.ncbi.nlm.nih.gov/pubmed/11721494> (2001)

- Rates between 0.8%⁸⁷⁹ - 1.4%⁸⁸⁰ - 9%⁸⁸¹ - 15%⁸⁸² - 32%⁸⁸³ -34%⁸⁸⁴ - 40%⁸⁸⁵ - 43%⁸⁸⁶ 887 - 47%⁸⁸⁸ - 54%⁸⁸⁹
 - Incidence varies by antibiotic and dosage⁸⁹⁰.
 - No standard for determining a JHR.
- May show up as worst MRIs⁸⁹¹ 892
- Can last for hours and reoccur⁸⁹³
- Associated with Gram-positive, Gram-negative or fungal organisms⁸⁹⁴
- Improves with olanzapine treatment⁸⁹⁵.
- Improves with dexamethasone treatment⁸⁹⁶
- Improves with antipyretic and anti-inflammatory agents⁸⁹⁷.
- Improves with pre-treatment with anti-tumour necrosis factor antibodies⁸⁹⁸ 899 900.
- Pentoxifylline does not have any effect⁹⁰¹.

⁸⁷⁹ <http://www.ncbi.nlm.nih.gov/pubmed/19411042> (2009)

⁸⁸⁰ <http://www.ncbi.nlm.nih.gov/pubmed/22607395> (2012)

⁸⁸¹ <http://www.ncbi.nlm.nih.gov/pubmed/21297087> (2010)

⁸⁸² <http://www.ncbi.nlm.nih.gov/pubmed/17412541> (2007)

⁸⁸³ <http://www.ncbi.nlm.nih.gov/pubmed/12380884> (2002)

⁸⁸⁴ <http://www.ncbi.nlm.nih.gov/pubmed/20825309> (2010)

⁸⁸⁵ <http://www.ncbi.nlm.nih.gov/pubmed/9794683> (1998)

⁸⁸⁶ <http://www.ncbi.nlm.nih.gov/pubmed/16222003> (2005)

⁸⁸⁷ <http://www.ncbi.nlm.nih.gov/pubmed/8511813> (1993)

⁸⁸⁸ <http://www.ncbi.nlm.nih.gov/pubmed/7784810> (1995)

⁸⁸⁹ <http://www.ncbi.nlm.nih.gov/pubmed/9455520> (1998 *)

⁸⁹⁰ <http://www.ncbi.nlm.nih.gov/pubmed/7784810> (1995)

⁸⁹¹ <http://www.ncbi.nlm.nih.gov/pubmed/21042805> (2011)

⁸⁹² <http://www.ncbi.nlm.nih.gov/pubmed/18302644> (2008)

⁸⁹³ <http://www.ncbi.nlm.nih.gov/pubmed/19040755> (2008)

⁸⁹⁴ <http://www.ncbi.nlm.nih.gov/pubmed/12122518> (2002)

⁸⁹⁵ <http://www.ncbi.nlm.nih.gov/pubmed/18635694> (2009)

⁸⁹⁶ <http://www.ncbi.nlm.nih.gov/pubmed/18302644> (2008)

⁸⁹⁷ <http://www.ncbi.nlm.nih.gov/pubmed/16288069> (2005)

⁸⁹⁸ <http://www.ncbi.nlm.nih.gov/pubmed/15896248> (2005)

⁸⁹⁹ <http://www.ncbi.nlm.nih.gov/pubmed/9093599> (1997 *)

⁹⁰⁰ <http://www.ncbi.nlm.nih.gov/pubmed/8663853> (1998 *)

⁹⁰¹ <http://www.ncbi.nlm.nih.gov/pubmed/8769625> (1996)

16 Genetics

The genetic aspect of CFS became visible with Dave Bergs identification of inherited coagulation abnormalities as part of the cocktail of events needed to create CFS. A 2011 study found familial clustering⁹⁰².

Over 65⁹⁰³ polymorphisms^{904 905 906 907 908 909 910 911 912 913 914 915 916 917 918 919 920} are associated with CFS with machine learning models^{921 922 923} producing reliable predictors of CFS⁹²⁴. Similar work is occurring with MCS^{925 926 927} and FM^{928 929 930 931}. Some of these polymorphisms are connected with the regulation of brain cytokines⁹³².

16.1 Gene Expression

- Higher in CFS⁹³³
 - Group A: Increases in mRNA for sensory and adrenergic receptors and a cytokine
 - Group B (orthostatic intolerance): Decreases in mRNA for α -2A
 - mRNA increases in metabolite-detecting receptors, abnormal increases in adrenergic receptors⁹³⁴

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- ⁹⁰² <http://www.ncbi.nlm.nih.gov/pubmed/21619629> (2011)
- ⁹⁰³ <http://www.ncbi.nlm.nih.gov/pubmed/21912186> (2011)
- ⁹⁰⁴ <http://www.ncbi.nlm.nih.gov/pubmed/21059181> (2011)
- ⁹⁰⁵ <http://www.ncbi.nlm.nih.gov/pubmed/19822091> (2009)
- ⁹⁰⁶ <http://www.ncbi.nlm.nih.gov/pubmed/20074440> (2009)
- ⁹⁰⁷ <http://www.ncbi.nlm.nih.gov/pubmed/20227423> (2010)
- ⁹⁰⁸ <http://www.ncbi.nlm.nih.gov/pubmed/19758204> (2009)
- ⁹⁰⁹ <http://www.ncbi.nlm.nih.gov/pubmed/18774769> (2008)
- ⁹¹⁰ <http://www.ncbi.nlm.nih.gov/pubmed/18079067> (2008)
- ⁹¹¹ <http://www.ncbi.nlm.nih.gov/pubmed/17561688> (2007)
- ⁹¹² <http://www.ncbi.nlm.nih.gov/pubmed/17547679> (2007)
- ⁹¹³ <http://www.ncbi.nlm.nih.gov/pubmed/16762155> (2006)
- ⁹¹⁴ <http://www.ncbi.nlm.nih.gov/pubmed/16740143> (2007)
- ⁹¹⁵ <http://www.ncbi.nlm.nih.gov/pubmed/16731592> (2007)
- ⁹¹⁶ <http://www.ncbi.nlm.nih.gov/pubmed/15554358> (2004)
- ⁹¹⁷ <http://www.ncbi.nlm.nih.gov/pubmed/14592408> (2003)
- ⁹¹⁸ <http://www.ncbi.nlm.nih.gov/pubmed/22110941> (2012)
- ⁹¹⁹ <http://www.ncbi.nlm.nih.gov/pubmed/17885758> (2008)
- ⁹²⁰ <http://www.ncbi.nlm.nih.gov/pubmed/21190576> (2010)
- ⁹²¹ <http://www.ncbi.nlm.nih.gov/pubmed/19772600> (2009)
- ⁹²² <http://www.ncbi.nlm.nih.gov/pubmed/19102713> (2009)
- ⁹²³ <http://www.ncbi.nlm.nih.gov/pubmed/18986552> (2008)
- ⁹²⁴ <http://www.ncbi.nlm.nih.gov/pubmed/22674373> (2011 *)
- ⁹²⁵ <http://www.ncbi.nlm.nih.gov/pubmed/21845158> (2011)
- ⁹²⁶ <http://www.ncbi.nlm.nih.gov/pubmed/20201826> (2009)
- ⁹²⁷ <http://www.ncbi.nlm.nih.gov/pubmed/20067442> (2010)
- ⁹²⁸ <http://www.ncbi.nlm.nih.gov/pubmed/21125150> (2010)
- ⁹²⁹ <http://www.ncbi.nlm.nih.gov/pubmed/17187510> (2007)
- ⁹³⁰ <http://www.ncbi.nlm.nih.gov/pubmed/20041150> (2009)
- ⁹³¹ <http://www.ncbi.nlm.nih.gov/pubmed/9076694> (1997)
- ⁹³² <http://www.ncbi.nlm.nih.gov/pubmed/21584188> (2011)
- ⁹³³ <http://www.ncbi.nlm.nih.gov/pubmed/21615807> (2012)

- Increased gene expression for metabolite detecting receptors, for sympathetic nervous system receptors and Immune System genes lasting from 0.5 to 48 hours after exercise⁹³⁵.

16.2 Evolutional Benefit for CFS Genes

Gene variations to become common imply that at some time in history it gave the carriers an advantage. For the CFS genes appear to be commonly activated when there is an immune response to an infection coupled with stress. One apparent benefit scenario is when a lethal infection is sweeping through a community. African communities' response to disease outbreaks in the area is to go into isolation and have no contact with anyone else. The symptoms of CFS put people into isolation, eliminating repeated exposures to the infection and result in a relatively larger percentage of CFS patients surviving. The apparent up-regulation of the immune system would further protect the individuals with this type of response. CFS are in one sense the persisters⁹³⁶, they become relatively dormant so that they survive when something attacks the community.

17 Pathogen Drill Downs

17.1 Chlamydia Pneumonia

- Seropositive rate was 45% seen in controls⁹³⁷
- Detected within atherosclerotic plaques and can induce the structural remodeling of the vessel wall⁹³⁸.
- Induces eNOS downregulation causing endothelial dysfunction⁹³⁹.
- Chlamydia can also be isolated from brain tissues of patients⁹⁴⁰
- Acute infections are recurrent infections⁹⁴¹
- Increased inflammatory activity⁹⁴²
- Activates platelets, leading to oxidation of low-density lipoproteins⁹⁴³
- Increased fibrinogen levels⁹⁴⁴
- Increased levels of cytokines IL-6, IL-8, IL-17, and IL-23.⁹⁴⁵, IL-10⁹⁴⁶, IL-1⁹⁴⁷
- Frequently found in patients with asthma⁹⁴⁸

⁹³⁴ <http://www.ncbi.nlm.nih.gov/pubmed/22210239> (2012)

⁹³⁵ <http://www.ncbi.nlm.nih.gov/pubmed/19647494> (2009)

⁹³⁶ See Pathogens persistence above.

⁹³⁷ <http://www.ncbi.nlm.nih.gov/pubmed/20016424> (2009)

⁹³⁸ <http://www.ncbi.nlm.nih.gov/pubmed/22214836> (2012)

⁹³⁹ <http://www.ncbi.nlm.nih.gov/pubmed/19443423> (2009)

⁹⁴⁰ <http://www.ncbi.nlm.nih.gov/pubmed/19673684> (2009)

⁹⁴¹ <http://www.ncbi.nlm.nih.gov/pubmed/9008746> (1996)

⁹⁴² <http://www.ncbi.nlm.nih.gov/pubmed/14962698> (2003)

⁹⁴³ <http://www.ncbi.nlm.nih.gov/pubmed/17459368> (2007)

⁹⁴⁴ <http://www.ncbi.nlm.nih.gov/pubmed/9597405> (1998)

⁹⁴⁵ <http://www.ncbi.nlm.nih.gov/pubmed/21803599> (2011)

⁹⁴⁶ <http://www.ncbi.nlm.nih.gov/pubmed/18602070> (2008)

⁹⁴⁷ <http://www.ncbi.nlm.nih.gov/pubmed/20393140> (2010)

18 Treatment 101 for CFS Patients

In the above chapters a lot of technical information was given – too much information to digest typically. This chapter consolidates to simple lists what has been demonstrated to definitely help with at least 40% of patients in studies.

18.1 Patient to Patient

18.2 Handling JHR

One of my symptoms for JHR was headaches that I rarely ever get.

Remedy	Effectiveness
Tumeric (600mg) + Piracetam (600mg)	5 star
500 (flushing) niacin	4 Star
45 minutes of exercise	1 Star
Doing nothing	0 Star

18.3 Anti-pathogens

Protocols:

- CPN: Chlamydia Pneumoniae Help, <http://www.cpnhelp.org/>
 - CPN-S: Stratton Protocol
 - CPN-W: Wheldon Protocol
 - CPN-P: Prowell Protocol
- CJ : CL Jadin

18.3.1 Non-prescription

18.3.1.1 Multiple

Artemisinin

- Potential application for the treatment of neuroinflammatory diseases.
- Reduces TNF- α , IL-6, MCP-1 and nitric oxide (NO) ⁹⁴⁹
- Reduces IL-1Beta⁹⁵⁰
- Effective against CMV^{951,952}

⁹⁴⁸ <http://www.ncbi.nlm.nih.gov/pubmed/21029940> (2010)

⁹⁴⁹ <http://www.ncbi.nlm.nih.gov/pubmed/22514713> (2012)

⁹⁵⁰ <http://www.ncbi.nlm.nih.gov/pubmed/21165548> (2011)

⁹⁵¹ <http://www.ncbi.nlm.nih.gov/pubmed/21904628> (2011)

- Effective against EBV⁹⁵³

Turmeric

- Effective against EBV^{954 955}
- Inhibits H. pylori⁹⁵⁶

18.3.1.2 Antiviral

The following have demonstrated antiviral activity:

18.3.1.3 Antibacterial

There have been many published papers and conference presentations on the use of antibiotics for CFS. At my last survey, many reported remissions, most reported improvement and none reported adverse effect.

18.3.2 Prescription

Multiple

Antiviral

18.4 Gums

A very old remedy is Jerusalem Balsam⁹⁵⁷ that can be traced to at least 1719, and may date back to the days of the Pharaohs. It contains three gums that share similar characteristics.

18.5 Anti-biofilm Agents

- EDTA
- Serrapeptase

18.6 Fibrinolytic Agents

A fibrinolytic agent is something that dissolves or breaks down fibrin deposit. Fibrin is deemed to be the main cause for high blood viscosity. Many of these items also increase the penetration of anti-pathogens into tissue. If you are on anti-pathogens, their use may significantly increase JHR. The following are non-prescription agents:

- Alpha Lipoic Acid
- Bromelain

⁹⁵² <http://www.ncbi.nlm.nih.gov/pubmed/21843554> (2011)

⁹⁵³ <http://www.ncbi.nlm.nih.gov/pubmed/18699744> (2008)

⁹⁵⁴ <http://www.ncbi.nlm.nih.gov/pubmed/11884218> (2002)

⁹⁵⁵ <http://www.ncbi.nlm.nih.gov/pubmed/9457037> (1998)

⁹⁵⁶ <http://www.ncbi.nlm.nih.gov/pubmed/19204190> (2009)

⁹⁵⁷ <http://www.ncbi.nlm.nih.gov/pubmed/15963667> (2005)

- Lumbrokinase
- Nattokinase
- Serrapeptase

18.6.1 Supplements

- CoQ 10⁹⁵⁸
- DHEA⁹⁵⁹
- Ginseng⁹⁶⁰

19 Some Anecdotal Observations

19.1 Muscle Aches

There are two treatments to these aches that may be applied concurrently.

- Magnesium and Malic Acid⁹⁶¹. This may be done by tablets of Magnesium Malate or by Magnesium Citrate with a glass of apple juice. I found that the latter worked better for me.

19.2 Use of Anti-biofilm Agents

- EDTA
- Serrapeptase

- Fibrinolytic Agents.

19.3 Sore throat

The most effective treatment to ease a sore throat is Licorice in the form of spezzatina. Allow one at a time to dissolve slowly in the mouth. After 2 or three, relief can last several hours. The reason that it may work is that it reduces the cytokines that provokes the sore throat. Capsules of licorice extract did not have this effect.

19.4 Controlling JHR from anti-pathogens

Whenever I start an antibiotic, I avoid all potenziators for 72 hours prior to start. I will attempt to find out the half-life of the antibiotic and when the peak concentration after taking occurs (T_{Max}). Peak

⁹⁵⁸ <http://www.ncbi.nlm.nih.gov/pubmed/15889950> (2005)

⁹⁵⁹ <http://www.ncbi.nlm.nih.gov/pubmed/15889950> (2005)

⁹⁶⁰ <http://www.ncbi.nlm.nih.gov/pubmed/15889950> (2005)

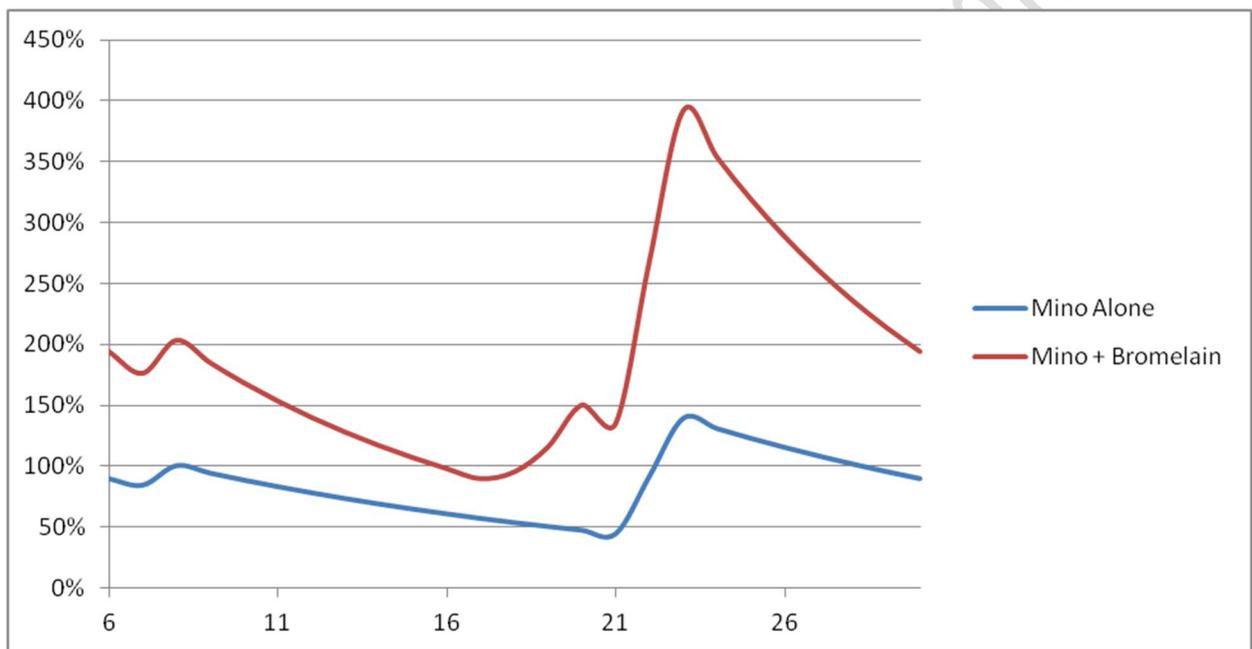
⁹⁶¹ <http://www.ncbi.nlm.nih.gov/pubmed/8587088> (1995)

concentration is generally delayed if taken with food. From this information, I attempt to schedule peak antibiotic concentration just after bed-time and sleep through most of any JHR.

For example, taking 100 mg of minocycline twice a day and taking bromelain (which increases the penetration by 220%⁹⁶²) results in the following pattern:

- 100 mg at 6am
- 100 mg at 9pm
- Bromelain at 2pm

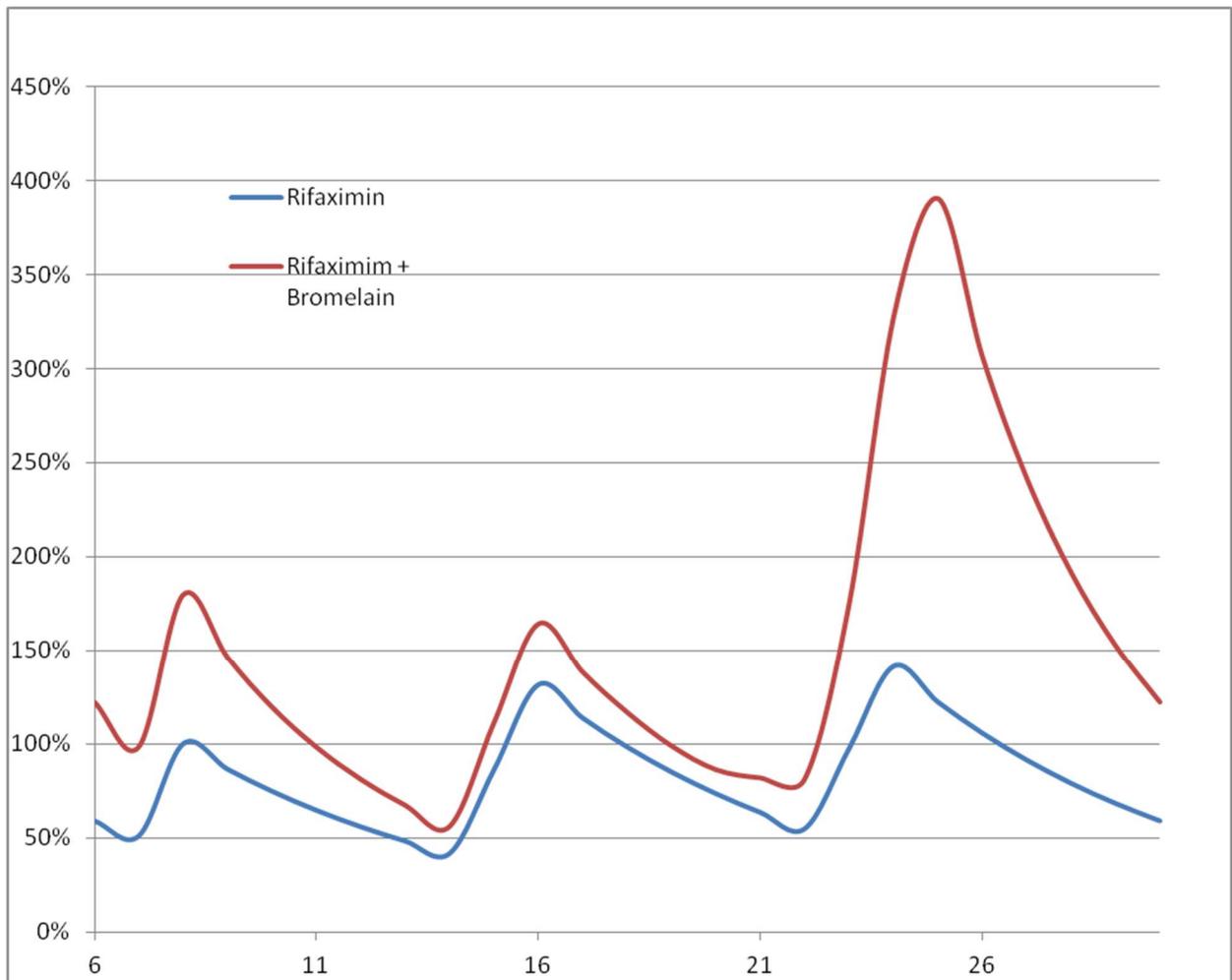
Doing some calculations in Excel, I ended up with the following concentration charts for minocycline during a day (6am until 6am the next day(30)). The result is



With a different antibiotic with three times a day, I ended calculating the following pattern (assuming similar amount of potentiation):

- 6 am – antibiotics
- 2 pm - antibiotics
- 10 pm - antibiotics
- 7 pm - bromelain

⁹⁶² <http://www.ncbi.nlm.nih.gov/pubmed/7001087> (1980)



A rule of thumb is:

- Take the potentiator 4-6 hrs before bedtime, once a day.
- Take the antibiotic 1 hr before bedtime.

Substance	Time to Max Concentration (MaxT)	Half-Life
Minocycline ⁹⁶³	2 hr	11-23 hrs
Doxycycline ⁹⁶⁴	2.6 hr	16 hrs
Tigecycline ⁹⁶⁵		37-67 hr
Amoxicillin ⁹⁶⁶		1 hr
Levofloxacin ⁹⁶⁷	1 hr ⁹⁶⁸	6-8 hrs
Erythromycin ⁹⁶⁹		1 hr
Clarithromycin ⁹⁷⁰		3 hr
Azithromycin ⁹⁷¹		40 hr
Rifampin ⁹⁷²	2 hr	5 hr
Bromelain ⁹⁷³	1 hr	6-9 hrs
Nattokinase ⁹⁷⁴		8 hrs

19.4.1 Known Potentators

The following have been demonstrated to increase the tissue concentration of various antibiotics:

- Bromelain
- Serrapeptase
- Nattokinase
- Lumbrokinase

The amount of increase is dose dependent, so to increase the degree of penetration you simply increase the dosage (within safe limits).

My personal experience suggests that EDTA increases JHR. The likely mechanism is breaking down protective biofilms exposing more of the pathogen.

20 Vocabulary

ALA: See Alpha Lipoic Acid.

Alpha Lipoic Acid (ALA):

Anti-viral

⁹⁶³ <http://www.drugs.com/pro/minocycline.html>

⁹⁶⁴ <http://www.drugs.com/pro/Doxycycline.html>

⁹⁶⁵ <http://aac.asm.org/content/49/1/220>

⁹⁶⁶ <http://www.emedexpert.com/facts/amoxicillin-facts.shtml>

⁹⁶⁷ <http://www.emedexpert.com/facts/levofloxacin-facts.shtml>

⁹⁶⁸ <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1315976/> (2005)

⁹⁶⁹ <http://www.emedexpert.com/compare/macrolides.shtml>

⁹⁷⁰ <http://www.emedexpert.com/compare/macrolides.shtml>

⁹⁷¹ <http://www.emedexpert.com/compare/macrolides.shtml>

⁹⁷² <http://www.drugs.com/pro/xifaxan.html>

⁹⁷³ [http://nopr.niscair.res.in/bitstream/123456789/5694/1/NPR%207\(4\)%20359-363.pdf](http://nopr.niscair.res.in/bitstream/123456789/5694/1/NPR%207(4)%20359-363.pdf)

⁹⁷⁴ http://www.cnmwellness.com/wp-content/uploads/2008/12/art_nattokinase_2.pdf

CCFP: see Chronic Ciguatera Fish Poisoning

C-reactive protein (CRP): a protein found in the blood that is elevated in response to inflammation.

CF: See Chronic Fatigue

CFS: See Chronic Fatigue Syndrome

Chronic Fatigue (CF):

Chronic Fatigue Syndrome (CFS):

CRP: see C-reactive protein.

Chronic Ciguatera Fish Poisoning (CCFP)^[W]: a foodborne illness caused by eating some reef fish contaminated with toxins originally produced by dinoflagellates.

EPO: See Evening Primrose Oil

Evening Primrose Oil (EPO):

IL-6: See Interleukin-6

Interleukin-6 (IL-6):

ME: See Myalgic Encephalomyelitis

Myalgic Encephalomyelitis:

Natural Killer Cells:

NK: See Natural Killer Cells

PEM: see Post-Exertional Malaise

Post-Exertional Malaise (PEM):

TBRF: see Tick-borne relapsing fever

Tick-borne relapsing fever (TBRF): Often misidentified as Lyme⁹⁷⁵.

TNF- α : see Tumor Necrosis Factor- α

Tumor Necrosis Factor- α (TNF- α),

Anti-bacterial

⁹⁷⁵ <http://www.ncbi.nlm.nih.gov/pubmed/9455520> (1998 *)

Mycoplasma pneumoniae : neurological impacts⁹⁷⁶

21 Further Information Sources

Lyndonville News (<http://www.davidsbell.com/>) : This is maintained by a MD, David Bell, that had a major CFS outbreak in his community. David is a noted CFS researcher and pediatrician. Lyndonville news is a regular web-based newsletter.

22 Short Bibliography

Web Documents:

Low Level Activation of Coagulation with Coagulopathies in the Etiology of CFS / FM and Chronic Illnesses. An Explanatory Model Revisited. DE BERG, LH BERG and HH.HARRISON;

23 <http://www.investinme.org/Documents/Journals/Journal%20of%20IIME%20Vol%206%20Issue%201%20Screen.pdf>

24 Speculations on Contributing Factors

24.1 Methylation issues

Hyperhomocysteinaemia is characterized by an abnormally large level of [homocysteine](#) in the [blood](#). Elevated levels have been associated with various disease states. It is associated with deficiency in B₆, B₉, and B₁₂. It is associated with thrombosis (blood clots).

24.1.1 A1298C

Do impact on stress⁹⁷⁷

The presence of homozygous MTHFR A1298C mutation was significantly associated with deep venous thrombosis. [<http://www.ncbi.nlm.nih.gov/pubmed/21080081> (2011)]. High rate seen (but not statistically significant) for prothrombin G20210A (which I also have).

On pubmed, 58 citations on "G20210A A1298C"

⁹⁷⁶ <http://www.ncbi.nlm.nih.gov/pubmed/11170938> (2001)

⁹⁷⁷ <http://www.ncbi.nlm.nih.gov/pubmed/22128864> (2012)

25 FM

25.1 Amitriptyline

A tricyclic antidepressant is a serotonin-norepinephrine reuptake inhibitor, with strong actions on the serotonin transporter and moderate effects on the norepinephrine transporter.

25.2 Duloxetine

FDA approved for treatment of FM. It is a serotonin-norepinephrine reuptake inhibitor (SNRI)

25.3 Pregabalin

FDA approved for treatment of FM. It is an anticonvulsant drug used for neuropathic pain

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