Diagnosing and Treating Infections in ME/CFS
Using Medications in ME/CFS

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RMS Stockholm Sweden
Diagnosing and Treating Infections in ME/CFS Patients

- It is unclear if infections act as a triggering factor for the disease or if they may be opportunistic and develop as a consequence of impaired immunity.

- Persistent infections can contribute to the maintenance of the disease and to the worsening of symptoms.
Common Pathogens Associated with ME/CFS

- **Bacterial**
  - Mycoplasma
  - Chlamydia

- **Viral**
  - Epstein-Barr Virus (EBV)
  - Cytomegalovirus (CMV)
  - HHV-6 and 7
  - Parvovirus
  - Enteroviruses
# Common Bacterial Infections Observed in Patients with ME/CFS

<table>
<thead>
<tr>
<th>Bacterial Infection</th>
<th>Test</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycoplasma</td>
<td>Serology and PCR</td>
<td>Prolonged antibiotic treatment</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>Serology and PCR</td>
<td>Prolonged antibiotic treatment</td>
</tr>
</tbody>
</table>
Bacterial Imbalance

- Intestinal Dysbiosis
  - Defined as a breakdown in the balance between putative species of “protective” versus “harmful” intestinal bacteria
  - Leads to leaky gut syndrome
Leaky Gut Syndrome

- Leaky gut occurs when the intestinal and/or bowel is hyperpermeable.
- Low tolerance to alcohol is presumed by some to be an indication of leaky gut syndrome.
- Leaky gut syndrome is an inducer of chronic low grade systemic inflammation.
Consequences of Leaky Gut Syndrome and Interrelationship with CFS

LEAKY GUT

- Presence in Blood of Bacterial LPS Through TOLL-Like Receptors
- Mycoses
- Undigested Proteins and Fat in Stool
- LPS of Intestinal Bacteria in Blood

PKR Activation

PGE2
- Inflammatory Syndrome
- Peripheral Vasoconstriction
- Thrombocytes
- Blood Viscosity
- PMS

Extracellular
- iNOS
- NO
- Gastric Reflux / Impaired Memory
- Th1: NK Cell Toxicity and T-Cell Toxicity
- Mycoses / Neuropenia
- Reactivation of Herpes Viruses
- Slowed Gastric Emptying
- Chlamydial Infections
- Low Blood Pressure
- Peripheral Vasoconstriction
- Low Intracellular NO

COX2
- Chronic Gastritis
- Inflammatory Syndrome
- Low NK Number / Low NK Activity
- Infections
- Metals in Body
- Other Toxins

B Cell Activation
- Short Term Antibody Levels
- Long Term Exhaustion
- Antibody Production

Kenny De Meirleir, M.D., Ph.D. Professor of Physiology and Medicine Vrije Universiteit Brussel
Leaky Gut Syndrome Diagnosis

- Laboratory findings in ME/CFS patients with leaky gut:
  - IgA and IgM for intestinal aerobic bacteria in serum
  - High plasma lipopolysaccharide levels in serum
  - High leukocyte ELASTASE activity in PBMCs
  - GI gastrin and small bowel biopsy

Kenny De Meirleir, M.D., Ph.D. Professor of Physiology and Medicine Vrije Universiteit Brussel
Leaky Gut Syndrome Treatment

- Reoccurring antibiotic combination therapy with alternating substances
  - One occurrence for 8-10 days per month or 21 days consecutively
    - Erythromycin
    - Clarithromycin
    - Xifaxan

- Probiotics - to rebuild the gut bacteria culture, but also for recovering it after each treatment
  - VSL-3
  - Mutaflor

- The treatment suppresses overgrowth, but does not eradicate an entire type of bacteria

- Leaky gut diet

Kenny De Meirleir, M.D., Ph.D. Professor of Physiology and Medicine Vrije Universiteit Brussel
## Common Viral Infections Observed in Patients with ME/CFS

<table>
<thead>
<tr>
<th>Virus</th>
<th>Test</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBV</td>
<td>Serology and PCR</td>
<td>Antiviral and/or immunological therapy</td>
</tr>
<tr>
<td>CMV</td>
<td>Serology, antigenemia, culture, PCR</td>
<td>Antiviral and/or immunological therapy</td>
</tr>
<tr>
<td>HHV-6</td>
<td>Serology, antigenemia, culture, PCR</td>
<td>Antiviral and/or immunological therapy</td>
</tr>
<tr>
<td>HHV-7</td>
<td>Serology, antigenemia, culture, PCR</td>
<td>Antiviral and/or immunological therapy</td>
</tr>
<tr>
<td>Parvovirus</td>
<td>IgG, IgM, PCR</td>
<td>IVIG</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>Serology</td>
<td>Oxymatrine</td>
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</tbody>
</table>
Detecting Herpes in CSF in Encephalopathic Patients: A Clinical Algorithm

CDC 1994 and 2003 Canadian Consensus Definitions Fulfilled

Prominent CNS Symptoms

Abnormal MRI/SPECT Scan

Abnormal Cerebral Spinal Fluid
  • Increased Opening Pressure on Lumbar Puncture
  • Increased Total Protein
    • Lymphocytosis

Positive Viral Culture/PCR
Prominent CNS Symptoms

- Headaches
- Neurocognitive impairments
  - Word finding
  - Short term memory
- Paresthesias
- Autonomic dysfunction
Magnetic Resonance Images (MRI)

Increased $T_2$-weighted images in high white matter tracts
Abnormal Cerebral Spinal Fluid

- Increased opening pressure on lumbar puncture
- Increased total protein (myelin basic protein)
- Lymphocytosis
## Characteristics of CSF with and without HHV-6 Infection

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CSF without HHV-6 infection</th>
<th>CSF with HHV-6 infection</th>
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</thead>
<tbody>
<tr>
<td>Oligoclonal banding</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>Total protein</td>
<td>Normal</td>
<td>↑</td>
</tr>
<tr>
<td>Myelin basic protein</td>
<td>normal</td>
<td>↑</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>normal</td>
<td>↑</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>normal</td>
<td>↑</td>
</tr>
<tr>
<td>Opening pressure</td>
<td>normal</td>
<td>↑</td>
</tr>
</tbody>
</table>
Viruses in CSF of ME/CFS Patients

- 44/279 (16%) ME/CFS patients positive for virus in spinal fluid
  - 1 EBV (HHV-4)
  - 1 CMV (HHV-5)
  - 42 HHV-6, all variant A
  - 0 HHV-7
  - 0 HHV-8
## Number of Patients Treated with Anti-Herpes Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>N total</th>
<th>N female</th>
<th>N male</th>
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<tr>
<td>Ganciclovir</td>
<td>4</td>
<td>4</td>
<td>0</td>
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<tr>
<td>Foscarnet</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>40</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Transfer Factor</td>
<td>47</td>
<td>37</td>
<td>10</td>
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<tr>
<td>Poly[l]-Poly[C\textsubscript{12}U]</td>
<td>586</td>
<td>n/a</td>
<td>n/a</td>
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</tbody>
</table>
Patient 1566

- First seen in 1996
- Classic symptoms of ME/CFS
- Initial diagnosis of “Tahoe flu”
- Seizures accompanied by MRI UBOs
- Serum and spinal fluid positive for HHV6 A
- Germ line CIHHV6 verified 2007
- Developed clonal TCRγ rearrangement 04/2007
- Cidofovir therapy in 2007 followed by improvement in symptoms and reduced HHV6 viral load
Patient 1566

<table>
<thead>
<tr>
<th></th>
<th>Pre-Cidofovir</th>
<th>Post-Cidofovir</th>
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<tbody>
<tr>
<td>CSF</td>
<td>PCR HHV6A +</td>
<td>HHV6A -</td>
</tr>
<tr>
<td>CSF</td>
<td>VIRAL LOAD</td>
<td>Undetected</td>
</tr>
<tr>
<td>SERUM</td>
<td>PCR HHV6A+</td>
<td>HHV6A+</td>
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<tr>
<td>SERUM</td>
<td>VIRAL LOAD</td>
<td>3,000</td>
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</tbody>
</table>
Clinical Study

- Cross-Sectional Study of Leukotropic Herpes viruses in Patients with Post Infectious Fatigue

- Study goal
  - Identification of chronic active herpesvirus infections in individuals in order to prevent the misdiagnosis of “chronic fatigue syndrome” and thereby justify new intervention strategies, such as antiviral therapy

K Knox, D Carrigan, D Peterson 2010
Study Subjects

- 249 study subjects

- All subjects met the following criteria:
  - Canadian Consensus Document and CDC criteria for ME/CFS
  - Systemic signs and symptoms of an active, ongoing infection

K Knox, D Carrigan, D Peterson 2010
Methods for the Diagnosis of Human Herpesvirus Infections

- Detection of HHV-6 and HCMV
  - Viral isolation from PBL using human diploid fibroblasts as the viral target
  - Detection of viral DNA in serum or plasma by nested PCR

- Detection of active EBV virus
  - IgG antibody titers for specific viral proteins (EBV EBNA-1)
Detection of Herpesvirus Infections

- Detection of herpes virus infections by Immediate Early Protein Antigenemia (left)
- Detection of herpes virus infections by Immediate Early Protein Rapid Culture (right)

K Knox, D Carrigan, D Peterson 2010
Active Leukotropitic Herpes Virus Infections in Blood Samples from Patients with Post Infectious Fatigue

Percent of Patients Positive

<table>
<thead>
<tr>
<th></th>
<th>HHV-6</th>
<th>HCMV</th>
<th>EBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>54/194</td>
<td>71/249</td>
<td>79/153</td>
</tr>
</tbody>
</table>

1 Positive antigenemia or culture

2 EBNA-1 IgG titer >4000 units/ml

K Knox, D Carrigan, D Peterson 2010
Beta herpesvirus cohort

- 29% CMV+
- 9% CMV+ & HHV6+
  - N = 17/174
- 28% HHV6+
  - N = 54/194

Chi-Squared
CMV and HHV6:
P = .029

Gamma herpesvirus cohort

- 51% EBNA-1 Titers > 4000 units/mL
  - N = 79/153

K Knox, D Carrigan, D Peterson 2010
Cidofovir Treatment Reduces CMV Activity in Samples from 16 Treated Patients

K Knox, D Carrigan, D Peterson 2010
Cidofovir Treatment of Patients with Post-Infectious Fatigue

- Patient 7465
  - Rapid culture or antigenemia

<table>
<thead>
<tr>
<th>Months After Treatment</th>
<th>0</th>
<th>5</th>
<th>8</th>
<th>11</th>
<th>13</th>
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<tbody>
<tr>
<td>HCMV</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>HHV-6</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</table>

<table>
<thead>
<tr>
<th>Months After Treatment</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>10</th>
<th>13</th>
<th>18</th>
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<tbody>
<tr>
<td>HCMV</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HHV-6</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- Patient 7259
  - Rapid culture or antigenemia

K Knox, D Carrigan, D Peterson 2010
Study Conclusions

1. Active beta herpes virus infections and high EBNA-1 titers are often seen patients with post-infectious fatigue syndrome
2. Treatment with effective antiviral agents demonstrates suppression of viral activity
3. Future research studies should include long-term clinical follow-up of “antiviral responders”
4. Up to 30% of this sample may benefit from antiviral treatment

K Knox, D Carrigan, D Peterson 2010
Using Medications in ME/CFS
Medications for Treating ME/CFS

- There is no known cause and no known cure for ME/CFS
- There are no FDA or Health Canada approved drugs for treatment of ME/CFS
- Current available therapies only target one or more of the endocrinological, neurological, immunological or psychological symptoms related to ME/CFS
Medications for Treating ME/CFS

- A CDC study reported that ME/CFS patients use two times more drugs compared to controls.
- ME/CFS patients were more likely to use any drug category than controls.
- Pain relievers and vitamins/supplements were most commonly used in both groups.
- ME/CFS patients were more likely to use pain relievers, hormones, antidepressants, benzodiazepines, GI and CNS medications.

Jones JF, Nisenbaum R, Reeves WC. Medication Use by Persons With Chronic Fatigue Syndrome: Results of a Randomized Telephone Survey in Wichita, Kansas. BioMed Central Health Quality of Life Outcomes 2003;1:74
General Treatment Caveats

- No treatment strategies are universally effective
- ME/CFS patients are hypersensitive to medications
  - Start low, go slow
- Multiple medications are often required to address the numerous symptoms
  - If needed, make one medication change at a time, therefore the effectiveness and side effects of each medication can be determined
- Medications may need to be replaced periodically in order to avoid developing tolerance to medications
- Always keep the therapeutic regimen as safe, simple, effective and inexpensive as possible
Symptomatic Treatment

- ME/CFS patients present with different symptoms
- Determine which symptoms are of greatest concern and contribute most to dysfunction
- Identify co-morbid conditions
- Prioritize the symptoms and/or co-morbid conditions and tailor the management plan accordingly
- Adjust the treatment plan as needed
- Always evaluate and address new symptoms or deterioration
Prescription Medications

- Treatment is based on the symptomatology of ME/CFS
  1. Drugs to improve sleep
  2. Drugs to relieve pain
  3. Drugs to alter mood and/or cognition
  4. Drugs to treat endocrine and neuroendocrine abnormalities
  5. Immunological and antiviral therapies
  6. Other drugs

- ME/CFS patients are often hypersensitive to medications
  - Reduce dose to 1/2 to 1/3 the recommended dose*

1. Drugs to Improve Sleep

- Sleep sustainers - often used off-label to assist sleep
  - Trazodone
  - Doxepin
  - Cyclobenzaprine
  - Amitriptyline
  - Mirtazapine
  - Gabapentin

- Sedative/hypnotics - approved specifically for sleep
  - Zopiclone
  - Quetiapine

- Benzodiazepines
  - Clonazepam

- L-tryptophan
- Melatonin

2. Drugs to Relieve Pain

- Acetaminophen
- NSAIDs
  - Ibuprofen
  - Naproxen
- Cox-2 inhibitors
  - Celecoxib
- TCAs
  - Amitriptylline
  - Nortriptylline
  - Doxepin
- Muscle relaxants
  - Cyclobenzaprine
  - Baclofen
- Anticonvulsants
  - Gabapentin – for severe neuropathic pain
  - Pregabalin
- Narcotics/opiates – only if severe pain

3. Drugs to Alter Mood and/or Cognition

- Stimulants – improve fatigue
  - Methylphenidate
    - Randomized control trial (RCT)
    - 22% of pts improved concentration
    - 17% of pts decreased fatigue scores
  - Modafanil
  - Armodafinil
  - Dextroamphetamine
  - Amantadine
    - Side effects can be severe in ME/CFS patients

3. Drugs to Alter Mood and/or Cognition (continued)

- **SSRIs**
  - First line for depression treatment
  - Not usually effective in treating fatigue
  - May interfere with sleep

- **Fluoxetine**
  - RCT ineffective in Rx of depression in ME/CFS patients

- **Citalopram**

- **Paroxetine**

- **Sertraline**

- **Fluvoxamine**

3. Drugs to Alter Mood and/or Cognition (continued)

- SNRIs
  - Venlafaxine – may increase pain threshold
  - Duloxetine

- MAOIs
  - Moclobemide
    - Improves fatigue¹

- Other antidepressants
  - Bupropion
    - Showed improvement of depression in nine patients²

<table>
<thead>
<tr>
<th>MULTI-USE DRUGS</th>
<th>SLEEP</th>
<th>MOOD</th>
<th>PAIN</th>
<th>MIGRAINE</th>
<th>SIDE EFFECTS</th>
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<tbody>
<tr>
<td><strong>TCAs</strong></td>
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<tr>
<td>Amitriptyline</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>Weight gain, Orthostatic intolerance</td>
</tr>
<tr>
<td>Doxepin</td>
<td>+</td>
<td></td>
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<td></td>
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<tr>
<td><strong>Trazodone</strong></td>
<td>++++</td>
<td></td>
<td></td>
<td></td>
<td>Day sedation</td>
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<td><strong>SSRIs</strong></td>
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<tr>
<td>Fluoxetine, Sertraline, Citalopram</td>
<td>+/-</td>
<td>++++</td>
<td>+</td>
<td></td>
<td>Day sedation</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>++++</td>
<td>+</td>
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<td><strong>SNRIs</strong></td>
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<tr>
<td>Venlafaxine</td>
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<td>+</td>
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<td>Increase in diastolic BP</td>
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<td>Gabapentin</td>
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<td>++++</td>
<td>+</td>
<td>Brain fog</td>
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<td>++++</td>
<td>++</td>
<td>++++</td>
<td>+</td>
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<td><strong>Antipsychotics</strong></td>
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<tr>
<td>Quetiapine</td>
<td>++++</td>
<td>+++</td>
<td></td>
<td></td>
<td>Weight gain</td>
</tr>
</tbody>
</table>

Bateman L., Chronic Fatigue Syndrome/Fibromyalgia – Tips and Travails of Treatment – ProHealth
4. Drugs to Treat Endocrine and Neuroendocrine Abnormalities

- Hydrocortisone
- Fludrocortisone
- DHEA
- Galantamine
  - Increases acetylcholine leading to an increase in the activity of the HPA axis
  - RCT reported no significant differences between placebo and drug
- Melatonin
  - Some patients found an increase in physical function

5. Immunological and Antiviral Therapies

- **Immunoglobulin**
  - Gamma globulin
    - RCT – mixed results, high incidence of side effects

- **Ampligen (Poly I:Poly C<sub>12</sub>U)**
  - Approved in Canada, but not in US
  - Improves ME/CFS symptoms

- **Antivirals**
  - Acyclovir
  - Valacyclovir
  - Ganciclovir
  - Valganciclovir (Ganciclovir prodrug)
    - Significant improvement in patients with a preceding viral illness
  - Cidofovir
  - CMX001
  - Foscarnet

2. Kogelnik et al. Use of valganciclovir in patients with elevated antibody titers against Human Herpesvirus-6 (HHV-6) and Epstein-Barr Virus (EBV) who were experiencing central nervous system dysfunction including long-standing fatigue J Clin Virol. 2006 Dec;37 Suppl 1:S33-8
5. Immunological and Antiviral Therapies (continued)

DNA virus antivirals - Herpes viruses

- DNA synthesis inhibitor (HSV-1, HSV-2, VZV, EBV, CMV)
  - Thimidine kinase (TK) activated – purine analogue
    - Acyclovir/Valacyclovir
    - Ganciclovir/Valganciclovir
  - Not TK activated
    - Foscarnet – acyclovir and ganciclovir resistant

- Nucleic acid inhibitors
  - Cidofovir – acyclovir resistant herpes, CMV, VZV, anti-BK virus
CMX001 – Cidofovir PIM Conjugate

- CMX001 is a mimic of a naturally occurring lipid, lysolecithin, formed by linking a lipid to the phosphonate group of cidofovir.
- Designed to readily cross the intestinal wall and penetrate target cells before being cleaved to free the antiviral cidofovir.
- Improved Potency Demonstrated in Preclinical Studies.
- In cell culture assays, CMX001 is significantly more active than cidofovir against double-stranded DNA viruses including:
  - Orthopoxviruses (variola, monkeypox, vaccinia, cowpox, and ectromelia)
  - Herpes viruses (CMV, herpes simplex virus (HSV)-1,-2,-6,-8, HSV-2, varicella zoster virus (VZV), Epstein-Barr virus (EBV))
  - Multiple adenoviruses
5. Immunological and Antiviral Therapies (continued)

**Poly I: Poly C$_{12}$U**
- An immune stimulator and viral modulator
- Double-stranded RNA compound
- New protocol revisions
- Clinical trials
  - AMP 516 – 2004 RCT, double-blind, phase III
  - AMP 511 – ongoing, open-label, phase III
6. Other Drugs

- Orthostatic intolerance
  - Volume expansion
    - Sodium chloride – salt, IV normal saline
    - Fludrocortisone
  - Beta blockers
    - Pindolol
    - Atenolol
  - Alpha-1 agonists
    - Midodrine
  - Paroxetine (SSRI) – only use if the above Rx do not work

Medication Summary

- Create an individualized drug regimen
- Prioritize health concerns
  - Urgent health issues
  - Co-morbid conditions
  - Disruptive and disabling symptoms
- The goal of any treatment plan is to optimize health in order to optimize function
- Adjust medications as needed
- Balance the beneficial effects of medications against their adverse effects
- Address new symptoms if they develop